

PCT/EP04/011964



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EP04/11964

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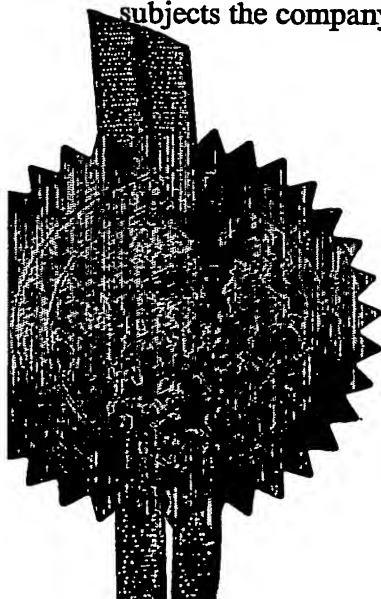
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P01/7700 0.00-0324895.2

Request for grant of a patent

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The Patent Office
Cardiff Road
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1. Your reference

DES/JW/PB60566P

2. Patent application number

(The Patent Office will fill in his part)

0324895.2

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

473587003

United Kingdom

4. Title of the invention

Compounds

5. Name of your agent (*if you have one*)

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Patents ADP number (*if you know it*)

Corporate Intellectual Property

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (*if you know it*) the or each application number

Country	Priority application number (<i>if you know it</i>)	Date of filing (<i>day / month / year</i>)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (<i>day / month / year</i>)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer yes if:*

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is named as an applicant, or
 - c) any named applicant is a corporate body
- See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
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Continuation sheets of this form
Description
Claim(s)
Abstract
Drawings

53
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10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature K Rutter WANN Date 24-Oct-03

12. Name and daytime telephone number of person to contact in the United Kingdom

K Rutter 01279 644396

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COMPOUNDS

This invention relates to heterocyclic compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of conditions mediated by the action of PGE₂ at the EP₁ receptor and conditions mediated by the action of thromboxane on the TP receptor. The invention also relates to compounds having activity at both the EP₁ and TP receptors.

The EP₁ receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE₂. PGE₂ also has affinity for the other EP receptors (types EP₂, EP₃ and EP₄). The EP₁ receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP₁ receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications*, Folco, Samuelsson, Macclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function*, S Narumiya et al, *Physiological Reviews* 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology*, 1994, 112, 735- 740 suggests that Prostaglandin E₂ (PGE₂) exerts allodynia through the EP₁ receptor subtype and hyperalgesia through EP₂ and EP₃ receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation*, 2001, 107 (3), 325 shows that in the EP₁ knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP₁ receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar et al in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP₁ receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDs and/or COX-2 inhibitors.

Certain compounds of the present invention also exhibit antagonism at the TP receptor.

5 The TP (also known as TxA_2) receptor is a prostenoid receptor subtype stimulated by the endogenous mediator thromboxane. Activation of this receptor results in various physiological actions primarily incurred by its platelet aggregatory and smooth muscle constricting effects, thus opposing those of prostacyclin receptor activation.

10 TP receptors have been identified in human kidneys (G.P. Brown *et al*, *Prostaglandins and other lipid mediators*, 1999, 57, 179-188) in the glomerulus and extraglomerular vascular tissue. Activation of TP receptors constricts glomerular capillaries and suppresses glomerular filtration rates (M.D. Breyer *et al*, *Current Opinion in Nephrology and Hypertension*, 2000, 9, 23-29), indicating that TP receptor antagonists could be useful for renal dysfunction in glomerulonephritis, diabetes mellitus and sepsis.

15 Activation of TP receptors induces bronchoconstriction, increase in microvascular permeability, formation of mucosal oedema and mucus secretion, typical characteristic features of bronchial asthma (T. Obata *et al*, *Clinical Review of Allergy*, 1994, 12(1), 79-93). TP antagonists have been investigated as potential asthma treatments resulting in, for example, orally active Seratrodist (AA-2414) (S. Terao *et al*, *Yakugaku Zasshi*, 1999, 119(5), 377-390). Ramatroban is another TP receptor antagonist currently undergoing phase III clinical trials as an anti-asthmatic compound.

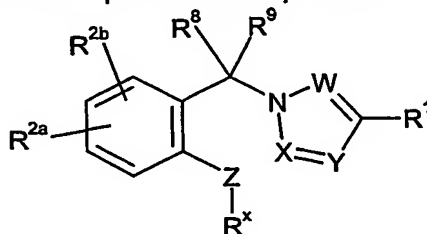
20 Antagonists at the TP receptor have been shown to have a gastroprotective effect. In rats it has been shown that SQ 33961 and BM 13505 inhibit gastric lesions induced by taurocholate acid, aspirin or indomethacin (E.H. Ogletree *et al*, *Journal of Pharmacology and Experimental Therapeutics*, 192, 263(1), 374-380.

30 In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE_2 -induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor. WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

35 It is now suggested that a novel group of pyrazole derivatives surprisingly are selective for the EP_1 receptor over the EP_3 receptor, and are therefore indicated to be useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors. Such conditions include pain, or inflammatory, immunological, bone, neurodegenerative or renal disorders.

40 It is also suggested that this novel group of pyrazole derivatives are antagonists at the TP receptor and are therefore indicated to be useful in treating conditions mediated by the action of thromboxane at the TP receptor. Such conditions include renal disorders, asthma and gastric lesions.

Accordingly the present invention provides compounds of formula (I):



(I)

wherein:

- 5 W represents N or CR¹⁰ wherein R¹⁰ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
X represents N or CR¹¹ wherein R¹¹ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
Y represents N or CR¹² wherein R¹² represents hydrogen, halogen, CH₃ or CF₃;
- 10 Z represents O, S, SO or SO₂;
R¹ represents CO₂R⁴, CONR⁵R⁶, CH₂CO₂H, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;
R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶ or optionally substituted heteroaryl;
- 15 R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR⁴, O and SO_n, wherein n is 0, 1 or 2; or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;
- 20 R⁴ represents hydrogen or an optionally substituted alkyl;
R⁵ represents hydrogen or an optionally substituted alkyl;
R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR⁷;
- 25 R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
R⁸ and R⁹ are independently selected from hydrogen, fluorine or alkyl, or R⁸ and R⁹ together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-alkyl;
- 30 wherein Q^a and Q^b are each independently selected from hydrogen, CH₃ and fluorine; or derivatives thereof.

- 35 Suitable examples of the five membered ring comprising W, X and Y are pyrrole, pyrazole, tetrazole, 2H-1,2,3-triazole and 1,2,4-triazole. Particular examples include pyrrole and pyrazole.

Suitably W is CH.

Suitably X includes CCH₃, CH and C-thienyl.

5 Suitably Y includes CH and CF.

Preferably R¹ represents CO₂R⁴. More preferably R¹ represents CO₂H.

A particular example of Z is O.

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When R^x represents optionally substituted alkyl this group is preferably C₁₋₈alkyl, for example butyl or *iso*-butyl.

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When R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl, suitably R^x includes optionally substituted CH₂-heterocyclyl e.g. CH₂-pyridyl, optionally substituted CH₂-bicyclic heterocyclyl or optionally substituted CH₂-aryl e.g. optionally substituted CH₂-phenyl. Optional substituents for CH₂-phenyl include one, two or three, preferably one or two substituents selected from Cl, Br, F, CF₃, NO₂, C₁₋₄alkyl and OC₁₋₄alkyl.

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Suitably R⁴ includes hydrogen and C₁₋₆alkyl.

Suitably R⁵ includes hydrogen and C₁₋₆alkyl.

25 Suitably R⁶ includes hydrogen and C₁₋₆alkyl.

Suitably R⁷ includes hydrogen and C₁₋₆alkyl.

Suitably R⁸ includes hydrogen.

30

Suitably R⁹ includes CH₃ and hydrogen.

Suitably R¹⁰ include hydrogen.

35 Suitably R¹¹ includes hydrogen, CH₃ and heterocyclyl, e.g. thienyl.

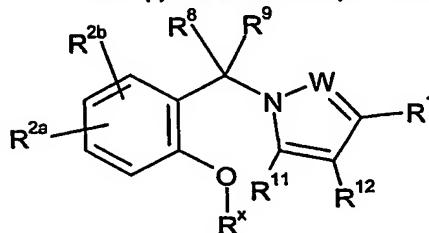
Suitably R¹² includes hydrogen, halo, e.g. fluorine.

An example of Q^a is hydrogen.

40

An example of Q^b is hydrogen.

In one aspect, compounds of formula (I) include compounds of formula (Ia):



(Ia)

wherein:

W is N or CR¹⁰;

5 R¹ is CO₂H;

R^{2a} and R^{2b} are independently selected from hydrogen, halo, optionally substituted C₁₋₆alkyl e.g. C₁₋₄alkyl and CF₃, and OC₁₋₆alkyl;

R^x is selected from CH₂-pyridyl, C₁₋₆alkyl or CH₂Ph wherein Ph is substituted by R^{3a}, R^{3b} and R^{3c};

10 R^{3a}, R^{3b} and R^{3c} are independently selected from hydrogen, halo, NO₂, optionally substituted C₁₋₆alkoxy, e.g. OCH₃ and optionally substituted C₁₋₆alkyl, e.g. CH₃ and CF₃; R⁸ and R⁹ are independently selected from hydrogen, fluorine or C₁₋₃alkyl, or R⁸ and R⁹ together with the carbon to which they are attached form a C₃₋₆cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-C₁₋₆alkyl;

15 R¹⁰ is selected from hydrogen, halogen, and optionally substituted C₁₋₈alkyl e.g. CH₃ and CF₃;

R¹¹ is selected from hydrogen, halogen, optionally substituted C₁₋₈alkyl e.g. Me and CF₃ and heterocyclyl e.g. thienyl; and

20 R¹² is selected from hydrogen, halogen e.g. fluorine, and optionally substituted alkyl e.g. CH₃ and CF₃; or derivatives thereof.

Compounds of formula (I) include the compounds of examples 1 to 62 and derivatives thereof.

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Preferably compounds are selective for EP₁ over EP₃. More preferably the compounds are 100 fold selective, more preferably 1000 fold selective for EP₁ over EP₃.

Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

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The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any

other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I).

- 5 It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

- 10 Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particular examples include the ammonium, calcium, magnesium, 15 potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, 20 N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic 25 acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

- 30 Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, 35 cyclohexylsulfamic, phosphoric and nitric acids.

- The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the 40 compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

- 5 Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

The terms "halogen" or "halo" are used to represent fluorine, chlorine, bromine or iodine.

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The term "alkyl" means a straight, branched or cyclic chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof such as cyclohexylmethyl and cyclopentylmethyl. Unless otherwise defined, preferably "alkyl" is C₁₋

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alkyl, more preferably "alkyl" is C₁₋₆alkyl.

The term "alkoxy" means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group. Preferably "alkoxy" is C₁₋₆ alkoxy.

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The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents, preferably one or two substituents. Examples of 5- membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

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The term "aryl" as a group or part of a group means a 5- or 6- membered aromatic ring, for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be optionally substituted by one or more substituents, for example up to 4, 3 or 2 substituents. Preferably the aryl group is phenyl.

35

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents, for example up to 3 or up to 2

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substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothieryl, indolyl, and indazolyl.

5

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl.

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When the heteroatom nitrogen replaces a carbon atom in an alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group, the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C₁₋₆alkyl, preferably hydrogen and C₁₋₆alkyl, more preferably hydrogen.

20

Optional substituents for alkyl groups include OH, CO₂R⁴, NR⁴R⁵, (O), OC₁₋₆alkyl or halo, wherein R⁴ and R⁵ are as herein before defined for compounds of formula (I). An alkyl group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents.

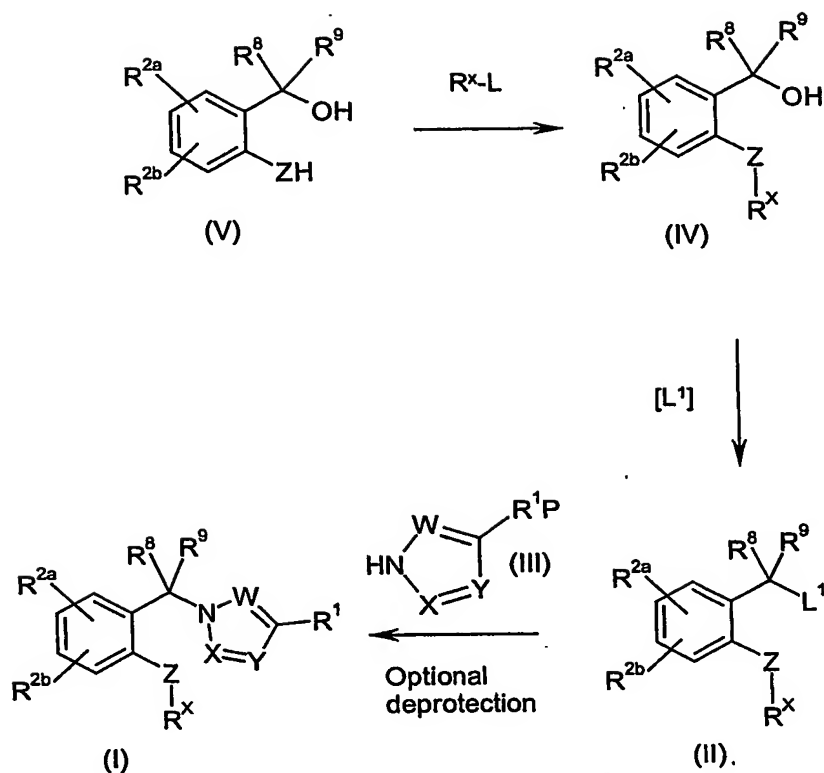
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Unless otherwise defined, optional substituents for aryl, heteroaryl or heterocyclyl moieties as a group or part of a group are selected from optionally substituted C₁₋₆alkyl, optionally substituted C₁₋₆alkoxy and halogen. Alternative optional substituents include C₁₋₆alkyl, C₁₋₆alkoxy and halogen.

30

Compounds of formula (I) can be prepared as set forth in the following schemes and in the examples. The following processes form another aspect of the present invention.

For example, compounds of formula (I) may be prepared by the general route below:



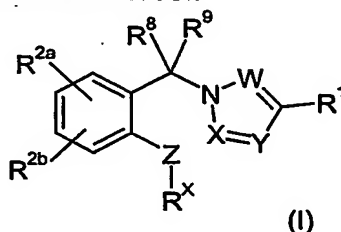
wherein L and L^1 are leaving groups, for example halo e.g. bromo; and $W, X, Y, Z, R^{2a}, R^{2b}, R^1, R^8, R^9$, and R^x are as defined for compounds of formula (I), and P is an optional protecting group. The skilled person will recognise when the use of a protecting group is necessary. When R^1 is CO_2H , R^1P is suitably $CO_2C_{1-4}alkyl$ or optionally substituted benzyl.

Suitable reaction conditions for the reaction of an amine of formula (III) with a compound of formula (II) to give a compound of formula (I) include heating in a solvent, e.g. ethanol, in the presence of a base, e.g. potassium *tert*-butoxide.

Suitable reaction conditions for the preparation a compound of formula (II) include conventional methods for converting the hydroxy group of the compound of formula (IV) to a leaving group, for example when L^1 is Br , the compound of formula (IV) may be reacted with phosphorous tribromide in a solvent, e.g. dichloromethane, at reduced temperatures, e.g. less than $-10^\circ C$.

Suitable reaction conditions for the reaction of a compound of formula (V) with a compound R^x-L to give a compound of formula (IV) are known to those skilled in the art and include the use of a solvent e.g. a $C_{1-4}alcohol$ such as methanol or ethanol in the presence of a base, e.g. sodium hydroxide.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:

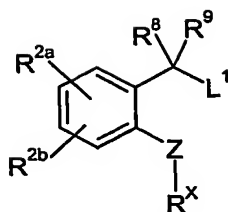


wherein:

- 5 W represents N or CR¹⁰ wherein R¹⁰ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
X represents N or CR¹¹ wherein R¹¹ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;
Y represents N or CR¹² wherein R¹² represents hydrogen, halogen, CH₃ or CF₃;
- 10 Z represents O, S, SO or SO₂;
R¹ represents CO₂R⁴, CONR⁵R⁶, CH₂CO₂H, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;
R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶
- 15 or optionally substituted heteroaryl;
R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR⁴, O and SO_n, wherein n is 0, 1 or 2; or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;
- 20 R⁴ represents hydrogen or an optionally substituted alkyl;
R⁵ represents hydrogen or an optionally substituted alkyl;
R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted
- 25 CQ^aQ^bheteroaryl or COR⁷;
R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
R⁸ and R⁹ are independently selected from hydrogen, fluorine or alkyl, or R⁸ and R⁹ together with the carbon to which they are attached form a cycloalkyl ring, optionally
- 30 containing up to one heteroatom selected from O, S, NH or N-alkyl;
wherein Q^a and Q^b are each independently selected from hydrogen, CH₃ and fluorine;

comprising:

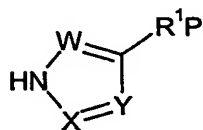
reacting a compound of formula (II):



(II)

wherein L^1 is a leaving group and Z , R^8 , R^9 , R^{2a} , R^{2b} , and R^x are as defined above for a compound of formula (I);

with a compound of formula (III):



(III)

wherein W , X , Y , and R^1 are as defined above for a compound of formula (I) and P is an optional protecting group;

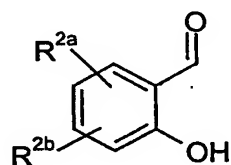
and where required, and in any order:

interconverting one substituent to another substituent; and/or

if necessary removing the optional protecting group; and/or

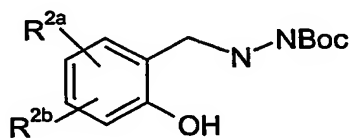
forming a derivative thereof.

Compounds of formula (I) wherein Z is O , W is N , X is CR^{10} , Y is CR^{11} , and R^1 is $COOH$ may be prepared by the general route below:

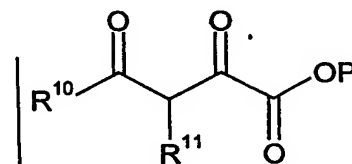


(IX)

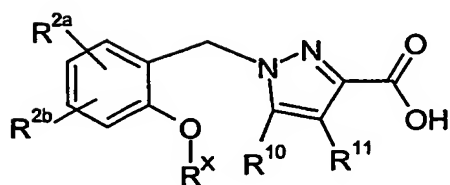
t-butyl carbazate



(VIII)

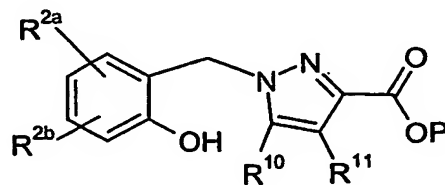


(VII)



(Ib)

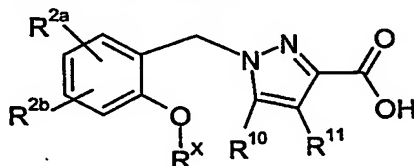
R^x-L
deprotect



(VI)

wherein L is a leaving group for example halo, e.g. bromo; P is a protecting group for example C₁₋₄ alkyl e.g. methyl or ethyl; and R^{2a}, R^{2b}, R¹⁰, R¹¹ and R^x are as defined for compounds of formula (Ia).

- 5 Accordingly the present invention also provides a process for the preparation of a compound of formula (Ib) or a derivative thereof:

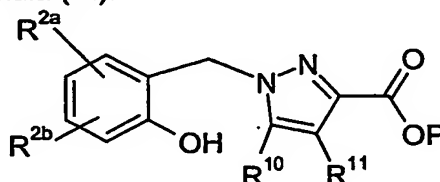


(Ib)

wherein:

- R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl,
 10 optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶
 or optionally substituted heteroaryl;
 R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms
 are optionally replaced by a group independently selected from NR⁴, O and SO_n, wherein n
 is 0, 1 or 2; or R^x may be optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted
 15 CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;
 R⁴ represents hydrogen or an optionally substituted alkyl;
 R⁵ represents hydrogen or an optionally substituted alkyl;
 R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl,
 optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted
 20 SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted
 CQ^aQ^bheteroaryl or COR⁷;
 R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or
 optionally substituted aryl;
 R¹⁰ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl,
 25 or optionally substituted heterocyclyl; and
 R¹¹ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl,
 or optionally substituted heterocyclyl;
 wherein Q^a and Q^b are each independently selected from hydrogen, CH₃ and fluorine;

- 30 comprising:
 reacting a compound of formula (VI):



(VI)

wherein R^{2a} , R^{2b} , R^{10} and R^{11} are as defined above for a compound of formula (Ib) and P is a protecting group;

with $R^x - L$ wherein R^x is as defined for compounds of formula (I) and L is a leaving group;

and where required, and in any order:

- 5 interconverting one substituent to another substituent; and/or
removing the protecting group; and/or
forming a derivative thereof.

- 10 When one or both of R^{10} and R^{11} is/are halogen, preferably the halogen group is introduced after the ring forming reaction of a compound of formula (VII) and (VIII). Suitable fluorination conditions are described in e.g. K. Makino *et al*, *J. Fluor. Chem*, 1988, 39, 435-440. Halogenation conditions are also reviewed in e.g. *Comprehensive heterocyclic chemistry. The structure, reactions, synthesis and uses of heterocyclic compounds*, A.R. Katritzky and C.W. Rees (Eds), vols 1-8, Pergamon Press, Oxford, 15 1984; *Comprehensive organic chemistry II. A review of the literature 1982-1995*, A.R. Katritzky, C.W. Rees, and E.F.V. Scriven (eds), vols 1-11, Pergamon Press, Oxford, 1996, and *Heterocyclic Chemistry*, 4th Edition, J.A. Joule and K. Mills, Blackwell Science, 2000.

- 20 Suitable reaction conditions for the reaction of a compound of formula (VI) with a compound R^x-L are known to those skilled in the art and include the use of a solvent e.g. a C_{1-4} alcohol such as methanol or ethanol in the presence of a base, e.g. sodium hydroxide. Suitable conditions for the deprotection of an ester to give the corresponding carboxylic acid are known to those skilled in the art.

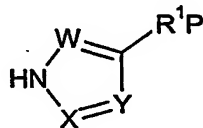
- 25 Suitable reaction conditions for the reaction of a compound of formula (VII) with a compound of formula (VIII) to give a pyrazole of formula (VI) will be apparent to the skilled person and include treatment with trifluoroacetic acid in a solvent, e.g. dichloromethane, at room temperature to remove the protecting group on the compound of formula (VIII) followed by cyclisation with (VII) in acidic conditions.

- 30 Suitable reaction conditions for the conversion of a salicylaldehyde of formula (IX) to a compound of formula (VIII) include reacting the salicylaldehyde with *tert*-butyl carbazate in the presence of acetic acid and sodium triacetoxymethylborohydride in a solvent such as dichloromethane.

- 35 Compounds R^x-L and compounds of formula (III), (V), (VII), (IX) and *t*-butyl carbazate are commercially available, or may be readily prepared from commercially available intermediates by methods known to those skilled in the art.

Compounds of formula R^x-L wherein L is as defined above and R^x is as defined for compounds of formula (I) are commercially available, or may be readily prepared by known transformations of commercially available compounds.

5 Compounds of formula (III):



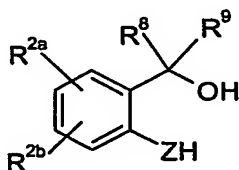
(III)

wherein W, X, Y and R^1 are as defined for compounds of formula (I) and P is an optional protecting group are commercially available, or may be prepared by conventional processes for the preparation of pyrroles, pyrazoles, triazoles and tetrazoles. The

10 preparation of pyrroles, pyrazoles, tetrazoles and triazoles is reviewed in e.g.

Comprehensive heterocyclic chemistry. The structure, reactions, synthesis and uses of heterocyclic compounds, A.R. Katritzky and C.W. Rees (Eds), vols 1-8, Pergamon Press, Oxford, 1984; *Comprehensive organic chemistry II. A review of the literature 1982-1995*, A.R. Katritzky, C.W. Rees, and E.F.V. Scriven (eds), vols 1-11, Pergamon Press, Oxford, 1996, and *Heterocyclic Chemistry*, 4th Edition, J.A. Joule and K. Mills, Blackwell Science, 2000.

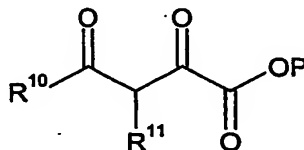
Compounds of formula (V):



(V)

20 wherein R^{2a} , R^{2b} , R^8 , and R^9 are as defined for compounds of formula (I) are commercially available, or may be prepared from commercially available intermediates by conventional methods. For example, processes for the preparation of 2-(hydroxymethyl)phenols are described in W.A. Sheppard, *J. Org. Chem.*, 1968, 33, 3297-3306.

25 Intermediates of formula (VII):

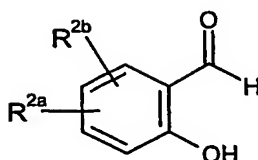


(VII)

wherein R^{10} and R^{11} are as defined for compounds of formula (Ia), and P is C_{1-4} alkyl e.g. methyl or ethyl, are commercially available or may be prepared from commercial

intermediates by known processes for the preparation of 1,3-diketones e.g. J. Royals, *J. Amer. Chem. Soc.* 1945, 67, 1508.

Intermediates of formula (IX):



wherein R^{2a} and R^{2b} are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available starting materials using methods as described in the examples. The preparation of aldehydes is reviewed in *The Chemistry of the Carbonyl Group*, S. Patai (Ed), Interscience, New York, 1966, and references cited therein.

Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, Richard Larock, *Comprehensive Organic Transformations*, 2nd edition, Wiley-VCH, ISBN 0-471-19031-4. Fluorination of pyrazoles is described in e.g. K. Makino *et al*, *J. Fluor. Chem*, 1988, 39, 435-440. When R^{10} is alkyl, the R^{10} group may be incorporated via C-metallation and alkylation as described in, for example, *Heterocyclic Chemistry*, 4th Edition, J.A. Joule and K. Mills, Blackwell Science, 2000.

For example, when R^x is p-methoxybenzyl, cleavage of the ether to give the phenol is carried out using, for example, using acid e.g. HCl/dioxane or using sodium methanethiolate. Conversion to another R^x group, for example a substituted benzyl group, may be effected by reaction of the phenol with a suitable substituted benzyl bromide. The skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When R^x is benzyl, cleavage of the ether to give the phenol may be carried out by hydrogenation according to known methods e.g. H_2 -Pd/C or NH_4CO_2H -Pd/C. The resulting phenol can then be converted to another group R^x as described above.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic

synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

5

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

15 The compounds of the invention bind to the EP₁ receptor and they are therefore considered to be useful in treating conditions mediated by the action of PGE₂ at EP₁ receptors.

20 Conditions mediated by the action of PGE₂ at EP₁ receptors include pain; fever; inflammation; immunological diseases; abnormal platelet function diseases; impotence or erectile dysfunction; bone disease; hemodynamic side effects of non-steroidal anti-inflammatory drugs; cardiovascular diseases; neurodegenerative diseases and neurodegeneration; neurodegeneration following trauma; tinnitus; dependence on a dependence-inducing agent; complications of Type I diabetes; and kidney dysfunction.

25

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are considered to be useful as analgesics. They are therefore considered useful in the treatment or prevention of pain.

30 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are considered useful as analgesics to treat acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, pain associated with cancer and fibromyalgia, pain associated with migraine, tension headache and cluster headaches, and pain associated with functional bowel disorders, non-cardiac chest pain and non-ulcer dyspepsia.

35

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are considered useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer

40

dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

5 The compounds of the invention are considered to be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes
10 include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of
15 neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased
20 sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

25 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of fever.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases
30 such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional
35 ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, scleroderma, myaesthesia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus
40 erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of immunological diseases such as autoimmune

diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

5 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of diseases relating to abnormal platelet function (e.g. occlusive vascular diseases).

10 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful for the preparation of a drug with diuretic action.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of impotence or erectile dysfunction.

15 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially
20 urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

25 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of cardiovascular diseases such as hypertension or myocardial ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g.
30 septic shock).

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of neurodegenerative diseases and
35 neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with
40 ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of neuroprotection and in the treatment of

neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

5 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of tinnitus.

10 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

15 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

20 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also considered useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

25 The compounds of formula (I) and pharmaceutically acceptable derivatives thereof are also useful in the treatment of overactive bladder and urge incontinence.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

30 According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

35 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

40 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE₂ at EP₁ receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, inflammatory, immunological, bone,

neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

- 5 According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.
- 10 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.
- 15 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, inflammatory, immunological, bone, neurodegenerative or renal disorder.
- 20 According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.
- 25 The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.
- 30 Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

- 35 The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

40

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

- 5 For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously).

- 10 The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for
15 reconstitution with a suitable vehicle.

- The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the
20 compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

- 25 The EP₁ receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor
30 antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT₁ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; nicotinic acetyl choline (nACh) receptor modulators; glutamate receptor
35 modulators, for example modulators of the NR2B subtype; EP₄ receptor ligands; EP₂ receptor ligands; EP₃ receptor ligands; EP₄ antagonists; EP₂ antagonists and EP₃ antagonists; cannabinoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any
40 convenient route.

Additional COX-2 inhibitors are disclosed in US Patent Nos. 5,474,995 US5,633,272; US5,466,823, US6,310,099 and US6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

5

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

10 In addition to activity at the EP₁ receptor, the compounds of the present invention and pharmaceutically acceptable derivatives thereof exhibit antagonism of the TP receptor and are therefore indicated to be useful in treating conditions mediated by the action of thromboxane at the TP receptor.

15 In view of their antagonism of the TP receptor, the compounds of the invention and pharmaceutically acceptable derivatives thereof are indicated to be useful in the treatment of renal disorders, asthma, or gastric lesions.

20 Certain compounds of the invention are equipotent antagonists of the EP₁ and TP receptors.

The present invention therefore also provides a compound which is an equipotent antagonist of the TP receptor and the EP₁ receptor.

25 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of thromboxane at the TP receptor.

30 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of thromboxane at the TP receptor which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

35 According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from a renal disorder, asthma, or gastric lesions, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

40 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of thromboxane at the TP receptor.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a renal disorder, asthma, or gastric lesions.

In certain situations it is envisaged that the administration of a compound exhibiting antagonism of TP receptors in combination with a compound exhibiting antagonism of EP₁ receptors may be advantageously beneficial.

The present invention therefore also provides a composition comprising an EP₁ antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof.

According to a further aspect, we provide a combination comprising an EP₁ antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

The present invention also provides a combination comprising an EP₁ antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of pain, or inflammatory, immunological, bone, neurodegenerative or renal disorders.

The present invention further provides a combination comprising an EP₁ antagonist or a pharmaceutically acceptable derivative thereof and a TP antagonist or a pharmaceutically acceptable derivative thereof for use in the treatment of inflammatory pain, neuropathic pain or visceral pain.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject a combination comprising an effective amount of an EP₁ antagonist or a pharmaceutically acceptable derivative thereof and an effective amount of a TP antagonist or a pharmaceutically acceptable derivative thereof.

According to a yet further aspect of the invention we provide a method of treating a human or animal subject suffering from inflammatory pain, neuropathic pain or visceral pain which method comprises administering to said subject a combination comprising an effective amount of an EP₁ antagonist or a pharmaceutically acceptable derivative thereof and an effective amount of a TP antagonist or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use an EP₁ antagonist or a pharmaceutically acceptable derivative thereof in combination with a TP antagonist or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE₂ at EP₁ receptors.

5

According to another aspect of the invention we provide the use an EP₁ antagonist or a pharmaceutically acceptable derivative thereof in combination with a TP antagonist or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

10

According to another aspect of the invention we provide the use of use an EP₁ antagonist or a pharmaceutically acceptable derivative thereof in combination with a TP antagonist or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as inflammatory pain, neuropathic pain or visceral pain.

15

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

20

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

25

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

30
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The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

40

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

10 The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

EXAMPLES**Abbreviations**

- 5 Dimethylsulfoxide (DMSO); acetonitrile (MeCN); methanol (MeOH); Solid phase extraction (SPE); liquid chromatography/mass spectrometry (LCMS); NMR (nuclear magnetic resonance);

LCMS

10

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5µl
- Temp: RT

15

- UV Detection Range: 215 to 330nm
-

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient: Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

Mass Directed Autopreparation

20

Hardware:

Waters 600 gradient pump

Waters 2767 inject/collector

Waters Reagent Manager

25

Micromass ZMD mass spectrometer

Gilson Aspec - waste collector

Gilson 115 post-fraction UV detector

Software :

Micromass Masslynx version 4.0

30

Column

The column used is typically a Supelco LCABZ++ column whose dimensions are 20mm internal diameter by 100mm in length. The stationary phase particle size is 5µm.

Solvents:

A.: Aqueous solvent = Water + 0.1% Formic Acid

35

B: Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid

Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate

Needle rinse solvent = MeOH: Water: DMSO 80:10:10

The method used depends on the analytical retention time of the compound of interest.

- 5 15-minute runtime, which comprises a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.

MDP 1.5-2.2 = 0-30%B

MDP 2.0-2.8 = 5-30% B

MDP 2.5-3.0 = 15-55%B

- 10 MDP 2.8-4.0 = 30-80% B

MDP 3.8-5.5 = 50-90% B

Flow rate:

flow rate 20ml/min.

15

General Method 1

Preparation of 4-bromo-2-(bromomethyl)phenyl phenylmethyl ether (Intermediate A)



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a) {5-bromo-2-[(phenylmethyl)oxy]phenyl}methanol

4-bromo-2-(hydroxymethyl)phenol (10.15g, 50mmol) was dissolved in ethanol (100ml) and 2M sodium hydroxide (27.5ml, 55mmol). The resulting solution was stirred for 10 minutes. A solution of [benzyl bromide] (5.95ml, 50mmol) in ethanol (100ml) was added slowly and the resulting solution was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo*, the solution obtained diluted with water and extracted with dichloromethane. The combined organic layers were washed sequentially with a saturated solution of NaHCO₃ and water, dried (Na₂SO₄) filtered and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane to yield the title compound as a colourless oil (13.8g, 94%).

30

¹H NMR δ: 2.19 (1H, t), 4.71 (2H, d, J = 6.3Hz), 5.10 (2H, s), 6.82 (1H, d, J = 8.6Hz), 7.34-7.47 (7H, m).

b) 4-bromo-2-(bromomethyl)phenyl phenylmethyl ether (Intermediate A)

- 35 A solution of {5-bromo-2-[(phenylmethyl)oxy]phenyl}methanol (5.41g, 18.44mmol) in dichloromethane (30ml) was stirred under nitrogen and cooled to -10°C (ice/acetone). A solution of phosphorous tribromide (4.99g, 1.75ml, 18.44mmol) in dichloromethane (15ml) was added slowly at -10°C and the mixture warmed to -7°C and stirred for 15 mins. The

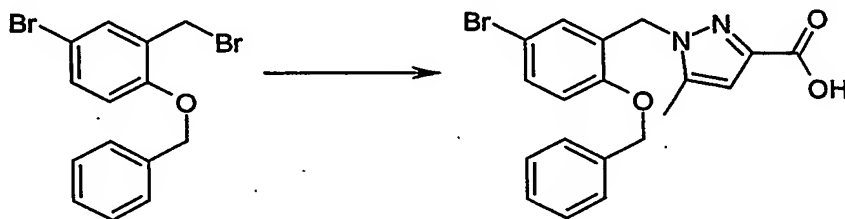
reaction was then allowed to warm to room temperature and was stirred overnight under nitrogen. The reaction mixture was cooled (ice/water bath) and a saturated sodium hydrogen carbonate solution (15.5ml) was then added slowly and the mixture diluted with dichloromethane and water. The organic phase was separated, washed with water then dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography with diethyl ether to yield the title compound as a white solid (5.53g, 84%).

^1H NMR δ : 4.54 (2H, s), 5.15 (2H, s), 6.81 (1H, d, $J = 8.8\text{Hz}$), 7.33-7.48 (7H, m)

10 General Method 2

Example 1: 1-({5-bromo-2-[(phenylmethyl)oxy]phenyl)methyl}-5-methyl-1H-pyrazole-3-carboxylic acid

Example 2: 1-({5-bromo-2-[(phenylmethyl)oxy]phenyl)methyl}-5-methyl-1H-pyrazole-5-carboxylic acid



Methyl 1H-pyrazole-3-carboxylate (12.61 mg, 0.1 mmol) was dissolved in a 0.105M solution of potassium *tert*-butoxide in ethanol (1ml, 11.78 mg, 0.105 mmol). After stirring at room temperature for 5 mins, a 0.1M solution of 4-bromo-2-(bromomethyl)phenyl phenylmethyl ether in ethanol (1ml, 35.6 mg, 0.1 mmol) was added and the resulting solution was stirred and heated at 60°C under nitrogen for 4hrs. After cooling the mixture was diluted with ethanol (1 ml) and a 0.5M solution of lithium hydroxide in water (1 ml, 11.97mg, 0.5mmol) was added. The mixture was stirred overnight at 40°C. After cooling 2M hydrochloric acid (0.3ml, 0.6mmol) was added and the mixture was diluted with water. Dichloromethane was added and the mixture stirred vigorously. The organic layer was separated and the solvent removed *in vacuo*. The residue was purified by mass directed autopurification to yield the title compounds.

1-({5-bromo-2-[(phenylmethyl)oxy]phenyl)methyl}-5-methyl-1H-pyrazole-3-carboxylic acid: (10.7mg, 27.6%).

^1H NMR δ : 5.08 (2H, s), 5.34 (2H, s), 6.72 (1H, d, $J = 2.2\text{Hz}$), 6.92 (1H, d, $J = 8.8\text{Hz}$), 7.23 (1H, d, $J = 2\text{Hz}$), 7.30-7.39 (6H, m), 7.45 (1H, d, $J = 2\text{Hz}$).

$t = 3.38$, $[\text{MH}^+] 387, 389$ $[\text{MH}^-] 385, 387$.

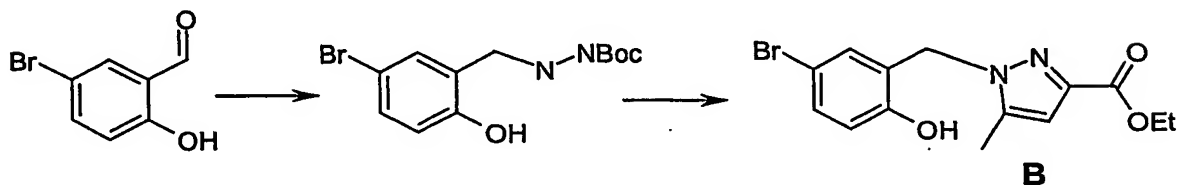
1-({5-bromo-2-[(phenylmethyl)oxy]phenyl)methyl}-5-methyl-1H-pyrazole-5-carboxylic acid (2.3mg, 5.9%)

^1H NMR δ : 5.08 (2H, s), 5.83 (2H, s), 6.54 (1H, d, $J = 2.01\text{Hz}$), 6.80 (1H, d, $J = 8.8\text{Hz}$), 6.90 (1H, d, $J = 2.01\text{Hz}$), 7.23-7.38 (6H, m), 7.53 (1H, d, $J = 1.76\text{Hz}$).

$t = 3.66$, $[\text{MH}^+] 387, 389$ $[\text{MH}^-] 385, 387$.

General Method 3

Preparation of ethyl 1-[(5-bromo-2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate (Intermediate B)



a) 1,1-dimethylethyl 2-[(5-bromo-2-hydroxyphenyl)methyl]hydrazinecarboxylate

5-bromo-2-hydroxybenzaldehyde (4.02g, 20mmol) was dissolved in dichloromethane (100ml). *Tert*-butyl carbazate (2.64g, 20mmol) and acetic acid (1.14ml, 1.2g, 20mmol) were added and the mixture was stirred under nitrogen for 30mins. Sodium triacetoxyborohydride (12.72g, 60mmol) was added portionwise and the resulting suspension was then stirred overnight under nitrogen. 2M hydrochloric acid (30ml, 60mmol) was added and the resulting solution was diluted with dichloromethane and water. The organic phase was separated, washed sequentially with brine and water then dried (Na_2SO_4) and evaporated to dryness to give the title compound as a white solid (6.01g, 94.7%)

^1H NMR δ : 1.48 (9H, s), 4.13 (2H, s), 4.40 (1H, br s), 6.15 (1H, br s), 6.78 (1H, d, J = 8.8Hz), 7.16 (1H, d, J = 2.26Hz), 7.29-7.32 (1H, m), 9.28 (1H, br s).
 t = 3.11, $[\text{MH}^+]$ 317, 319 $[\text{MH}^-]$ 315, 317.

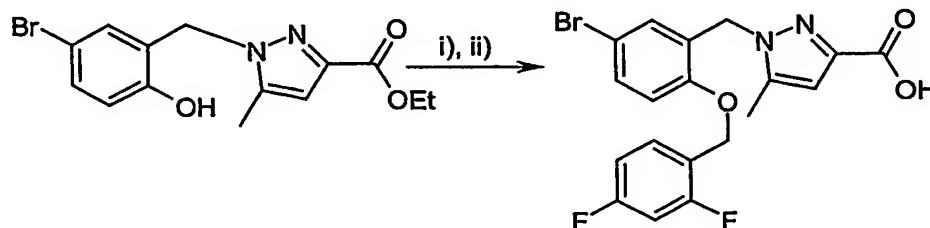
b) Ethyl 1-[(5-bromo-2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate (Intermediate B)

Trifluoroacetic acid (20ml) was added to 1,1-dimethylethyl 2-[(5-bromo-2-hydroxyphenyl)methyl]hydrazinecarboxylate (3.2g, 10mmol) in dichloromethane (40ml) and the reaction mixture stirred overnight at room temperature under nitrogen. The solvent was removed in vacuo and the residue obtained redissolved in acetic acid (20ml). The resulting solution was added dropwise to a solution of ethyl 2,4-dioxopentanoate (1.40ml, 1.58g, 10mmol) in acetic acid (10ml) and the reaction mixture was heated at reflux under nitrogen for 1h. The title compound crystallized upon cooling, was filtered, washed with acetic acid and dried under vacuo to give the title compound as white crystals (1.85g, 54.7%)

^1H NMR δ : 1.39 (3H, t, J = 7.15 Hz), 2.41 (3H, s), 4.34-4.40 (2H, q), 5.18 (2H, s), 6.58 (1H, s), 6.88 (1H, d, J = 8.5Hz), 7.24 (1H, d, J = 2.2Hz), 7.33 (1H, m), 9.56 (1H, br s).
 t = 3.17, $[\text{MH}^+]$ 339, 341 $[\text{MH}^-]$ 337, 339.

General Method 4

Example 3: 1-[(5-Bromo-2-[(2,4-difluorophenyl)methyl]oxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid



5

Ethyl 1-[(5-bromo-2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate (16.95mg, 0.05mmol) was dissolved in ethanol (0.5ml) and 2M sodium hydroxide (0.0275ml, 0.055mmol) and stirred at room temperature for 5 mins. 1-(bromomethyl)-2,4-difluorobenzene (10.35mg, 0.05mmol) in ethanol (0.5ml) was added and the reaction mixture heated under nitrogen at 70°C overnight. After cooling the mixture was diluted with ethanol (0.5 ml) and a 0.5M solution of lithium hydroxide in water (0.5 ml, 5.99mg, 0.25mmol) was added. The mixture was stirred at 40°C for 3 h. After cooling 2M hydrochloric acid (0.15ml, 0.3mmol) and the mixture was diluted with water.

10

Dichloromethane was added and the mixture stirred vigorously. The organic layer was separated and the solvent removed *in vacuo*. The residue was purified by mass directed autopurification to yield the title compound (18.4mg, 84.2%).

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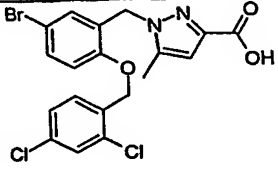
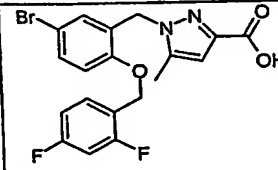
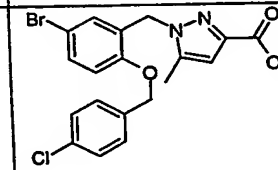
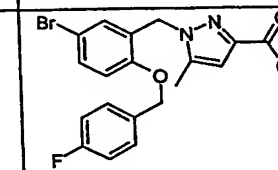
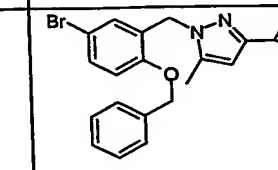
¹H NMR δ: 2.13 (3H, s), 5.10 (2H, s), 5.27 (2H, s), 6.55 (1H, s), 6.85 (1H, d, J = 2Hz), 6.89-6.97 (3H, m), 7.36-7.46 (2H, m).

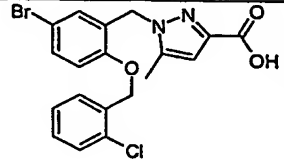
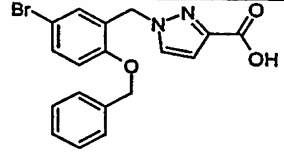
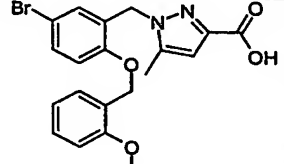
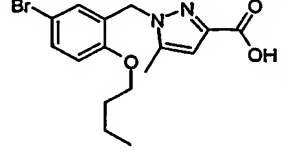
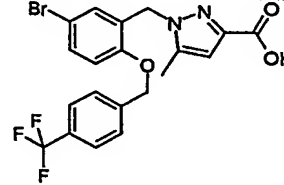
t = 3.48, [MH⁺] 437, 439 [MH⁻] 435, 437.

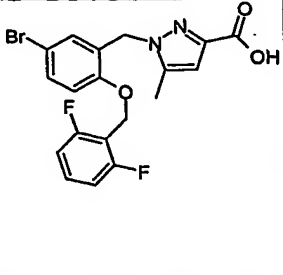
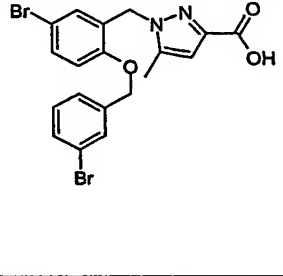
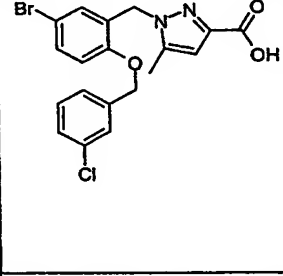
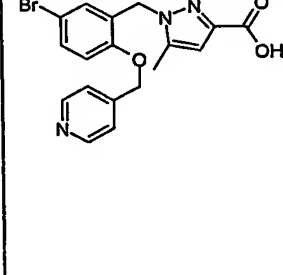
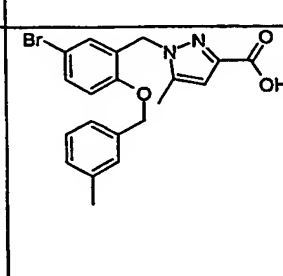
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Regioisomers: Elucidation of isolated structures where regioisomers can be formed (general methods 2 and 3) was determined by using either NMBC (heteronuclear multiple bond correlation); nOe (nuclear Overhauser effect) NMR techniques.

The following Examples were prepared from either Intermediate A or Intermediate B and Methods 2 or 4, and other appropriate starting materials.

4		Name	1-{5-bromo-2-[(2,4-dichlorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.15 (3H, s), 5.13 (2H, s), 5.31 (2H, s), 6.57 (1H, s), 6.80 (1H, d, J = 2.5Hz), 6.86 (1H, d, J = 8.8Hz), 7.28 (1H, m), 7.35 (1H, m), 7.39 (1H, d, J = 8.3Hz), 7.43 (1H, d, J = 2Hz)
		LCMS	t = 3.84, [MH ⁺] 467, 469, 471 [MH ⁻] 469, 471, 473
		Method	B and Method 4
5		Name	1-{5-bromo-2-[(2,4-difluorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.13 (3H, s), 5.10 (2H, s), 5.27 (2H, s), 6.55 (1H, s), 6.85 (1H, d, J = 2Hz), 6.89-6.97 (3H, m), 7.36-7.46 (2H, m)
		LCMS	t = 3.48, [MH ⁺] 437, 439 [MH ⁻] 435, 437
		Method	B and Method 4
6		Name	1-{5-bromo-2-[(4-chlorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.16 (3H, s), 5.10 (2H, s), 5.32 (2H, s), 6.57 (1H, s), 6.91 (1H, d, J = 2.2Hz), 6.99 (1H, d, J = 8.8Hz), 7.38-7.40 (5H, m)
		LCMS	t = 3.60, [MH ⁺] 435, 437 [MH ⁻] 433, 435
		Method	B and Method 4
7		Name	1-{5-bromo-2-[(4-fluorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.14 (3H, s), 5.09 (2H, s), 5.30 (2H, s), 6.57 (1H, s), 6.92 (1H, d, J = 2Hz), 7.00 (1H, d, J = 8.8Hz), 7.10 (2H, t, J = 8.8Hz), 7.38-7.44 (3H, m)
		LCMS	t = 3.44, [MH ⁺] 419, 421 [MH ⁻] 417, 419
		Method	B and Method 4
8		Name	1-[2-(benzyloxy)-5-bromobenzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.16 (3H, s), 5.08 (2H, s), 5.35 (2H, s), 6.67 (1H, s), 6.82-6.86 (2H, m), 7.34-7.43 (6H, m)
		LCMS	t = 3.42, [MH ⁺] 401, 403 [MH ⁻] 399, 401
		Method	B and Method 4

9		Name	1-{5-bromo-2-[(2-chlorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.13 (3H, s), 5.17 (2H, s), 5.32 (2H, s), 6.56 (1H, s), 6.80 (1H, d, J = 2.3Hz), 6.88 (1H, d, J = 8.8Hz), 7.25-7.43 (5H, m)
		LCMS	t = 3.66, [MH ⁺] 435, 437 [MH ⁻] 433, 435
		Method	B and Generic Method 4
10		Name	1-[2-(benzyloxy)-5-bromobenzyl]-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 5.08 (2H, s), 5.34 (2H, s), 6.72 (1H, d, J = 2.2Hz), 6.92 (1H, d, J = 8.8Hz), 7.23 (1H, d, J = 2Hz), 7.30-7.39 (6H, m), 7.45 (1H, d, J = 2Hz)
		LCMS	t = 3.38, [MH ⁺] 487, 489 [MH ⁻] 485, 487
		Method	A and Method 2
11		Name	1-{5-bromo-2-[(2-methoxybenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.12 (3H, s), 3.83 (3H, s), 5.10 (2H, s), 5.28 (2H, s), 6.54 (1H, s), 6.85 (1H, d), 6.91-6.96 (3H, m), 7.28-7.35 (3H, m)
		LCMS	t = 3.52, [MH ⁺] 431, 433 [MH ⁻] 429, 431
		Method	B and Method 4
12		Name	1-(5-bromo-2-butoxybenzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 0.96 (3H, t, J = 7.4Hz), 1.43-1.52 (2H, m), 1.73-1.80 (2H, m), 2.21 (3H, s), 3.99 (2H, t, J = 6.4Hz), 5.28 (2H, s), 6.58 (1H, s), 6.70 (1H, d, J = 2.2Hz), 6.78 (1H, d, J = 8.8Hz), 7.29-7.32 (1H, m)
		LCMS	t = 3.55, [MH ⁺] 367, 369 [MH ⁻] 365, 367
		Method	B and Method 4
13		Name	1-(5-bromo-2-[(4-(trifluoromethyl)benzyl)oxy]benzyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.18 (3H, s), 5.23 (2H, s), 5.36 (2H, s), 6.58 (1H, s), 6.91 (1H, d, J = 2.2Hz), 7.00 (1H, d, J = 8.8Hz), 7.38-7.41 (1H, m), 7.59 (2H, d, J = 8.3Hz), 7.68 (2H, d, J = 8.3Hz)
		LCMS	t = 3.61, [MH ⁺] 469, 471 [MH ⁻] 467, 469
		Method	B and Method 4

14		Name	1-{5-bromo-2-[(2,6-difluorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.08 (3H, s), 5.18 (2H, s), 5.21 (2H, s), 6.50 (1H, s), 6.94 (1H, d, J = 2Hz), 7.04 (2H, t, J = 8Hz), 7.14 (1H, d, J = 8.8Hz), 7.43-7.50 (2H, m)
		LCMS	t = 3.43, $[\text{MH}^+]$ 437, 439 $[\text{MH}^-]$ 435, 437
		Method	B and Method 4
15		Name	1-{5-bromo-2-[(3-bromobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.16 (3H, s), 5.08 (2H, s), 5.31 (2H, s), 6.58 (1H, s), 6.85 (1H, d, J = 2.1Hz), 6.89 (1H, d, J = 8.8Hz), 7.24-7.50 (5H, m)
		LCMS	t = 3.64, $[\text{MH}^+]$ 479, 481, 483 $[\text{MH}^-]$ 477, 479, 481
		Method	B and Method 4
16		Name	1-{5-bromo-2-[(3-chlorobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.16 (3H, s), 5.08 (2H, s), 5.31 (2H, s), 6.58 (1H, s), 6.85 (1H, d, J = 2Hz), 6.89 (1H, d, J = 8.8Hz), 7.27-7.36 (5H, m)
		LCMS	t = 3.59, $[\text{MH}^+]$ 435, 437 $[\text{MH}^-]$ 433, 435
		Method	B and Method 4
17		Name	1-[5-bromo-2-(pyridin-4-ylmethoxy)benzyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.23 (3H, s), 5.22 (2H, s), 5.40 (2H, s), 6.61 (1H, s), 6.87-6.89 (2H, m), 7.35-7.38 (1H, m), 7.51 (2H, d, J = 5.27Hz), 8.53 (2H, d, J = 4.52Hz)
		LCMS	t = 2.58, $[\text{MH}^+]$ 402, 404 $[\text{MH}^-]$ 400, 402
		Method	B and Method 4
18		Name	1-{5-bromo-2-[(3-methylbenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.12 (3H, s), 2.33 (3H, s), 5.03 (2H, s), 5.29 (2H, s), 6.56 (1H, s), 6.80 (1H, d, J = 2Hz), 6.85 (1H, d, J = 8.8Hz), 7.11-7.25 (4H, m), 7.30-7.33 (1H, m)
		LCMS	t = 3.58, $[\text{MH}^+]$ 415, 417 $[\text{MH}^-]$ 413, 415
		Method	B and Method 4

19		Name	1-{5-bromo-2-[(3-nitrobenzyl)oxy]benzyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	
		LCMS	t = 3.39, [MH+] 446, 448 [MH-] 444, 446
		Method	B and Method 4
20		Name	1-[2-(benzyloxy)-5-bromobenzyl]-5-thien-2-yl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 5.06 (2H, s), 5.50 (2H, s), 6.74 (1H, d, J = 1.8Hz), 6.88 (1H, d, J = 8.8Hz), 6.95 (1H, s), 7.00-7.02 (2H, m), 7.27-7.34 (6H, m), 7.43 (1H, d, J = 5.0Hz)
		LCMS	t = 3.83, [MH+] 469, 471 [MH-] 467, 469
		Method	A and Method 2
21		Name	1-[2-(benzyloxy)-5-bromobenzyl]-4-fluoro-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 5.07 (2H, s), 5.23 (2H, s), 6.90 (1H, d, J = 8.8Hz), 7.29-7.40 (8H, m)
		LCMS	t = 3.48, [MH+] 405, 407 [MH-] 403, 405
		Method	A and Method 2

The following intermediates were prepared from the appropriate starting materials according to Method 3.

5

C		Name	ethyl 1-[(5-chloro-2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate
		NMR	¹ H NMR δ: 1.26 (3H, t, J=6.9Hz), 2.27 (3H, s), 4.24 (2H, q, J=6.9Hz), 5.23 (2H, s), 6.58 (1H, s), 6.64 (1H, s), 6.86 (1H, d, J=8.5Hz), 7.17 (1H, d, J=8.5Hz), 10.18 (1H, s)
		LCMS	t=3.10, [MH+] 295, 297, [MH-] 295, 293
		Method	Method 3
D		Name	ethyl 1-[[2-hydroxy-5-(methoxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylate
		NMR	¹ H NMR δ: 1.39 (3H, t, J=7.2Hz), 2.40 (3H, s), 3.75 (3H, s), 4.37 (2H, q, J=6.9Hz), 5.21 (2H, s), 6.57 (1H, s), 6.70 (1H, d, J=3.0Hz), 6.81 (1H, dd, J=3.0 and 8.9Hz), 7.93 (1H, d, J=8.9Hz), 8.65 – 8.78 (1H, br s)
		LCMS	t=2.83, [MH+] 291, [MH-] 289
		Method	Method 3

E		Name	ethyl 1-[(2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate
		NMR	¹ H NMR δ: 1.39 (3H, t, J=7.2Hz), 2.40 (3H, s), 4.37 (2H, q, J=7.2Hz), 5.25 (2H, s), 6.57 (1H, s), 6.85 – 6.89 (1H, m), 6.99 (1H, dd, J=7.3 and 1.0Hz), 7.14 (1H, dd, J=7.5 and 1.5Hz), 7.24 (1H, dd, J=1.8 and 8.0Hz), 9.22 (1H, s)
		LCMS	t=2.85, [MH ⁺] 261
		Method	Method 3
F		Name	ethyl 1-[(5-fluoro-2-hydroxyphenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylate
		NMR	¹ H NMR δ: 1.39 (3H, t, J=7.2Hz), 2.40 (3H, s), 4.37 (2H, q, J=7.2Hz), 5.20 (2H, s), 6.59 (1H, s), 6.82 (dd, 1H, J=2.0 and 7.5Hz), 6.93 (2H, m)
		LCMS	t=2.92, [MH ⁺] 279, 280
		Method	Method 3

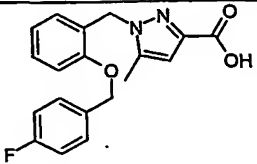
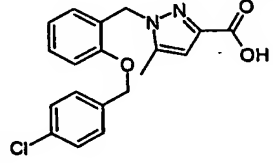
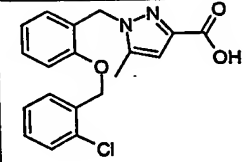
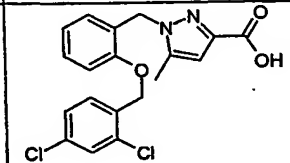
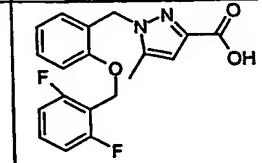
The following Examples were prepared from either Intermediate C, D, E or F according to Method 4.

22		Name	1-[(5-chloro-2-[(4-fluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.16 (3H, s), 5.04 (2H, s), 5.33 (2H, s), 6.67 (1H, s), 6.71 (1H, d, J= 2.5Hz), 6.87 (1H, d, J=8.8Hz), 7.10 (2H, t, J= 8.8Hz), 7.22 (1H, dd, J=8.8 and 2.5Hz), 7.36 (2H, dd, J=5.3 and 3.0Hz)
		LCMS	t=3.37, [MH ⁺] 375, 377, [MH ⁻] 373, 375
		Method	C and Method 4
23		Name	1-[(5-chloro-2-[(4-chlorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.15 (3H, s), 5.10 (2H, s), 5.31 (2H, s), 6.57 (1H, s), 6.76 (1H, d, J=2.5Hz), 7.03 (1H, d, J=8.8Hz), 7.24 (1H, dd, J=8.8 and 2.5Hz), 7.35 – 7.40 (4H, m)
		LCMS	t=3.51, [MH ⁺] 391, 393, [MH ⁻] 389, 391
		Method	C and Method 4

24		Name	1-[(5-chloro-2-[(2-chlorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.19 (3H, s), 5.19 (2H, s), 5.40 (2H, s), 6.67 (1H, s), 6.79 (1H, d, J =2.3Hz), 6.89 (1H, d, J =8.8Hz), 7.22 (1H, dd, J =8.8 and 2.3Hz), 7.30 – 7.32 (2H, m), 7.43 – 7.45 (2H, m)
		LCMS	t =3.53, [MH ⁺] 391, 393, [MH ⁻] 389, 391
		Method	C and Method 4
25		Name	1-[(5-chloro-2-[(2,4-dichlorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.13 (3H, s), 5.20 (2H, s), 5.27 (2H, s), 6.48 (1H, s), 6.85 (1H, d, J =2.5Hz), 7.16 (1H, d, J =8.8Hz), 7.38 (1H, dd, J =8.8 and 2.5Hz), 7.45 (1H, dd, J =8.3 and 2.0Hz), 7.62 (1H, d, J =8.3Hz), 7.71 (1H, d, J =2.3Hz)
		LCMS	t =3.75, [MH ⁺] 425, 427, 429, [MH ⁻] 423, 425, 427
		Method	C and Method 4
26		Name	1-[(5-chloro-2-[(2,6-difluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.13 (3H, s), 5.17 (2H, s), 5.27 (2H, s), 6.63 (1H, s), 6.73 (1H, d, J =2.5Hz), 6.95 – 7.02 (3H, m), 7.25 (1H, d, J =2.5Hz), 7.34 – 7.41 (1H, m)
		LCMS	t =3.36, [MH ⁺] 393, 395, [MH ⁻] 391, 393
		Method	C and Method 4
27		Name	1-[(5-chloro-2-[(2,4-difluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.17 (3H, s), 5.09 (2H, s), 5.33 (2H, s), 6.66 (1H, s), 6.71 (1H, d, J =2.5Hz), 6.86 – 6.94 (3H, m), 7.24 (1H, dd, J =8.8 and 2.5Hz), 7.36 – 7.42 (1H, m)
		LCMS	t =3.39, [MH ⁺] 393, 395, [MH ⁻] 391, 393
		Method	C and Method 4

28		Name	1-({5-chloro-2-[(phenylmethyl)oxy]phenyl}methyl)-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.16 (3H, s), 5.09 (2H, s), 5.36 (2H, s), 6.67 (1H, s), 6.71 (1H, d, $J=2.5\text{Hz}$), 6.89 (1H, d, $J=8.8\text{Hz}$), 7.21 (1H, dd, $J=8.8$ and 2.5Hz), 7.36 – 7.43 (5H, m)
		LCMS	$t=3.35$, $[\text{MH}^+]$ 357, 359, $[\text{MH}^-]$ 355, 357
		Method	C and Method 4
29		Name	1-[[2-[[[(4-fluorophenyl)methyl]oxy]-5-(methyloxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.15 (3H, s), 3.68 (3H, s), 5.01 (2H, s), 5.36 (2H, s), 6.34 (1H, d, $J=2.8\text{Hz}$), 6.65 (1H, s), 6.77 (1H, dd, $J=8.8$ and 3.0Hz), 6.87 (1H, d, $J=8.8\text{Hz}$), 7.06 – 7.11 (2H, m), 7.35 – 7.39 (2H, m)
		LCMS	$t=3.20$, $[\text{MH}^+]$ 371, $[\text{MH}^-]$ 369
		Method	D and Method 4
30		Name	1-[[2-[[[(4-chlorophenyl)methyl]oxy]-5-(methyloxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.17 (3H, s), 3.68 (3H, s), 5.02 (2H, s), 5.37 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$), 6.66 (1H, s), 6.76 (1H, dd, $J=8.8$ and 3.0Hz), 6.85 (1H, d, $J=9.0\text{Hz}$), 7.32 – 7.38 (4H, m)
		LCMS	$t=3.36$, $[\text{MH}^+]$ 387, 389, $[\text{MH}^-]$ 385, 387
		Method	D and Method 4
31		Name	1-[[2-[[[(2-chlorophenyl)methyl]oxy]-5-(methyloxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.18 (3H, s), 3.68 (3H, s), 5.16 (2H, s), 5.42 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$), 6.65 (1H, s), 6.78 (1H, dd, $J=8.8$ and 3.0Hz), 6.89 (1H, d, $J=9.0\text{Hz}$), 7.29 – 7.31 (2H, m), 7.42 – 7.44 (1H, m), 7.47 – 7.49 (1H, m)
		LCMS	$t=3.36$, $[\text{MH}^+]$ 387, 389, $[\text{MH}^-]$ 385, 387
		Method	D and Method 4

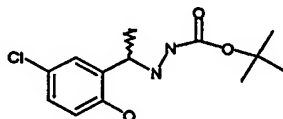
32		Name	1-[[2-[(2,4-dichlorophenyl)methyl]oxy]-5-(methoxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.13 (3H, s), 3.64 (3H, s), 5.12 (2H, s), 5.27 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$), 6.46 (1H, s), 6.86 (1H, dd, $J=9.0$ and 3.3Hz), 7.04 (1H, d, $J=8.8\text{Hz}$), 7.44 (1H, dd, $J=8.3$ and 2.0Hz), 7.63 (1H, d, $J=8.3$), 7.68 (1H, d, $J=2.0\text{Hz}$)
		LCMS	$t=3.57$, $[\text{MH}^+]$ 421, 423, $[\text{MH}^-]$ 419, 421
		Method	D and Method 4
33		Name	1-[[2-[(2,6-difluorophenyl)methyl]oxy]-5-(methoxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.12 (3H, s), 3.68 (3H, s), 5.13 (2H, s), 5.30 (2H, s), 6.34 (1H, d, $J=2.8\text{Hz}$), 6.61 (1H, s), 6.80 (1H, dd, $J=8.8$ and 3.0Hz), 6.93 – 7.03 (3H, m), 7.32 – 7.39 (1H, m)
		LCMS	$t=3.20$, $[\text{MH}^+]$ 389, $[\text{MH}^-]$ 387
		Method	I2 and Method 4
34		Name	1-[[2-[(2,4-difluorophenyl)methyl]oxy]-5-(methoxy)phenyl]methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.10 (3H, s), 3.64 (3H, s), 5.08 (2H, s), 5.20 (2H, s), 6.33 (1H, d, $J=3.0\text{Hz}$), 6.46 (1H, s), 6.85 (1H, dd, $J=9.0$ and 3.3Hz), 7.05 – 7.09 (2H, m), 7.21 – 7.27 (1H, m), 7.56 – 7.62 (1H, m)
		LCMS	$t=3.23$, $[\text{MH}^+]$ 389, $[\text{MH}^-]$ 387
		Method	D and Method 4
35		Name	5-methyl-1-[(5-(methoxy)-2-[(phenylmethyl)oxy]phenyl)methyl]-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : 2.14 (3H, s), 3.68 (3H, s), 5.06 (2H, s), 5.38 (2H, s), 6.34 (1H, d, $J=2.8\text{Hz}$), 6.65 (1H, s), 6.77 (1H, dd, $J=9.0$ and 3.0Hz), 6.89 (1H, d, $J=9.0\text{Hz}$), 7.35 – 7.41 (5H, m)
		LCMS	$t=3.18$, $[\text{MH}^+]$ 353, $[\text{MH}^-]$ 351
		Method	D and Method 4

36		Name	1-[(2-[(4-fluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.15 (3H, s), 5.15 (2H, s), 5.28 (2H, s), 6.48 (1H, s), 6.76 (1H, d, J=6.3Hz), 6.89 – 6.92 (1H, m), 7.11 (1H, d, J=8.0Hz), 7.18 – 7.23 (1H, m), 7.25 – 7.29 (1H, m), 7.48 – 7.52 (1H, m)
		LCMS	t=3.21, [MH ⁺] 341, [MH ⁻] 339
		Method	E and Method 4
37		Name	1-[(2-[(4-chlorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.17 (3H, s), 5.08 (2H, s), 5.39 (2H, s), 6.66 (1H, s), 6.77 (1H, d, J=7.5Hz), 6.90 – 6.93 (2H, m), 7.24 – 7.26 (2H, m), 7.33 – 7.39 (4H, m)
		LCMS	t=3.38, [MH ⁺] 357, 359, [MH ⁻] 355, 357
		Method	E and Method 4
38		Name	1-[(2-[(2-chlorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.18 (3H, s), 5.21 (2H, s), 5.44 (2H, s), 6.65 (1H, s), 6.77 (1H, d, J=7.0Hz), 6.91 – 6.98 (2H, m), 7.26 – 7.32 (3H, m), 7.43 – 7.49 (2H, m)
		LCMS	t=3.38, [MH ⁺] 357, 359, [MH ⁻] 355, 357
		Method	E and Method 4
39		Name	1-[(2-[(2,4-dichlorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.19 (3H, s), 5.17 (2H, s), 5.44 (2H, s), 6.66 (1H, s), 6.76 (1H, d, J=7.0Hz), 6.91 – 6.95 (2H, m), 7.25 – 7.31 (2H, m), 7.42 – 7.46 (2H, m)
		LCMS	t=3.58, [MH ⁺] 391, 393, [MH ⁻] 389, 391
		Method	E and Method 4
40		Name	1-[(2-[(2,6-difluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: 2.12 (3H, s), 5.18 (2H, s), 5.32 (2H, s), 6.61 (1H, s), 6.80 (1H, d, J=6.5Hz), 6.91 – 6.99 (3H, m), 7.08 (1H, d, J=8.3Hz), 7.29 – 7.39 (2H, m)
		LCMS	t=3.18, [MH ⁺] 359, [MH ⁻] 357
		Method	E and Method 4

41		Name	1-[(2-[(2,4-difluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.10 (3H, s), 5.16 (2H, s), 5.23 (2H, s), 6.46 (1H, s), 6.79 (1H, d, $J=7.5$ Hz), 6.92 – 6.95 (1H, m), 7.09 – 7.18 (2H, m), 7.29 – 7.34 (2H, m), 7.61 – 7.67 (1H, m)
		LCMS	$t=3.25$, [MH ⁺] 359, [MH ⁻] 357
		Method	E and Method 4
42		Name	5-methyl-1-[(2-[(phenylmethyl)oxy]phenyl)methyl]-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.15 (3H, s), 5.11 (2H, s), 5.41 (2H, s), 6.65 (1H, s), 6.78 (1H, d, $J=7.5$ Hz), 6.89 – 6.93 (1H, m), 6.97 (1H, d, $J=8.3$ Hz), 7.24 – 7.28 (1H, m), 7.36 – 7.42 (5H, m)
		LCMS	$t=3.19$, [MH ⁺] 323, [MH ⁻] 321
		Method	E and Method 4
43		Name	1-[(5-fluoro-2-[(4-fluorophenyl)methyl]oxy)phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.17 (3H, s), 5.04 (2H, s), 5.34 (2H, s), 6.46 (1H, dd, $J=3.0$ Hz and 8.8Hz), 6.67 (1H, s), 6.71 (1H, d, $J=2.5$ Hz), 6.87 – 6.90 (1H, m), 6.93 – 6.98 (1H, m), 7.08 – 7.12 (2H, m), 7.35 – 7.39 (2H, m)
		LCMS	$t=3.23$, [MH ⁺] 359, [MH ⁻] 357
		Method	F and Method 4
44		Name	1-[(2-[(4-chlorophenyl)methyl]oxy)-5-fluorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.18 (3H, s), 5.05 (2H, s), 5.37 (2H, s), 6.42 (1H, dd, $J=3.0$ and 8.5Hz), 6.67 (1H, s), 6.83 – 6.87 (1H, m), 6.90 – 6.95 (1H, m), 7.32 – 7.39 (4H, m)
		LCMS	$t=3.38$, [MH ⁺] 375, 377, [MH ⁻] 373, 375
		Method	F and Method 4

45		Name	1-[(2-[(2-chlorophenyl)methyl]oxy)-5-fluorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.14 (3H, s), 5.21 (2H, s), 5.34 (2H, s), 6.49 (1H, dd, J =2.8 and 8.8Hz), 6.56 (1H, s), 6.98 – 7.08 (2H, m), 7.31 – 7.36 (2H, m), 7.44 – 7.47 (1H, m), 7.49 – 7.51 (1H, m)
		LCMS	t =3.39, [MH ⁺] 375, 377, [MH ⁻] 373, 375
		Method	F and Method 4
46		Name	1-[(2-[(2,4-dichlorophenyl)methyl]oxy)-5-fluorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.13 (3H, s), 5.18 (2H, s), 5.28 (2H, s), 6.48 (1H, s), 6.59 (1H, d, J =8.8Hz), 7.16 (2H, d, J =5.0Hz), 7.46 (1H, dd, J =8.3 and 2.0Hz), 7.64 (1H, d, J =8.3Hz), 7.71 (1H, d, J =2.0Hz)
		LCMS	t =3.59, [MH ⁺] 409, 411, [MH ⁻] 407, 409
		Method	F and Method 4
47		Name	1-[(2-[(2,6-difluorophenyl)methyl]oxy)-5-fluorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.13 (3H, s), 5.16 (2H, s), 5.30 (2H, s), 6.46 (1H, dd, J =8.8 and 3.0Hz), 6.64 (1H, s), 6.95 – 7.04 (4H, m), 7.34 – 7.41 (1H, m)
		LCMS	t =3.21, [MH ⁺] 377, [MH ⁻] 375
		Method	F and Method 4
48		Name	1-[(2-[(2,4-difluorophenyl)methyl]oxy)-5-fluorophenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.18 (3H, s), 5.09 (2H, s), 5.35 (2H, s), 6.45 (1H, dd, J =8.8 and 2.8Hz), 6.67 (1H, s), 6.86 – 6.98 (4H, m), 7.38 – 7.44 (1H, m)
		LCMS	t =3.27, [MH ⁺] 377, [MH ⁻] 375
		Method	F and Method 4
49		Name	1-[(5-fluoro-2-[(phenylmethyl)oxy]phenyl)methyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ : 2.17 (3H, s), 5.08 (2H, s), 5.37 (2H, s), 6.44 (1H, dd, J =8.8 and 2.8Hz), 6.67 (1H, s), 6.87 – 6.96 (2H, m), 7.34 – 7.43 (5H, m)
		LCMS	t =3.22, [MH ⁺] 341, [MH ⁻] 339
		Method	F and Method 4

The intermediate 1,1-dimethylethyl 2-[(5-chloro-2-hydroxyphenyl)ethyl] - hydrazinecarboxylate was prepared from the appropriate ketone according to Method 3.

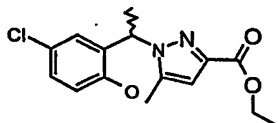


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^1H NMR (CDCl_3) δ : 1.41 (3H, d, $J=6.8\text{Hz}$), 1.48 (9H, s), 4.21-4.25 (1H, m), 6.23 (1H, br s), 6.77 (1H, d, $J = 8.6\text{Hz}$), 6.96 (1H, d, $J = 2.4\text{Hz}$), 7.11 (1H, dd, $J=8.6$ $J=2.3$ Hz).

10

The intermediate 1-[1-(5-chloro-2-hydroxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (G) was prepared from 1,1-dimethylethyl 2-[(5-chloro-2-hydroxyphenyl)ethyl]hydrazinecarboxylate according to Method 3.



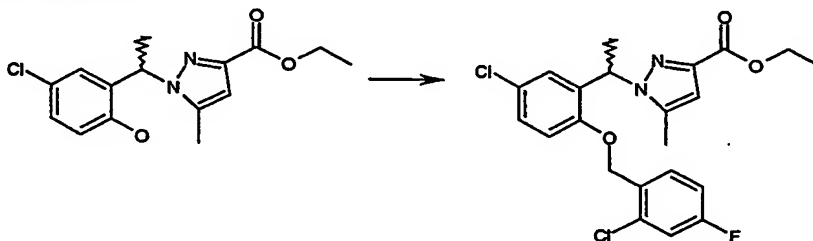
15

^1H NMR (CDCl_3) δ : 1.28 (3H, t, $J=7.1$ Hz), 1.71 (3H, d, $J= 6.8$ Hz), 2.20 (3H, s), 4.25 (2H, dq, $J=2.08$ $J= 7.1$ Hz), 5.81 (1H, q, $J=6.8$ Hz), 6.56 (1H, s), 6.77 (1H, d, $J=2.6$ Hz), 6.84 (1H, d, $J=8.6$ Hz), 7.14 (1H, dd, $J=2.6$ $J=8.6$ Hz), 10.15 (1H, s).

General Method 5

20

1-[1-(5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester



25

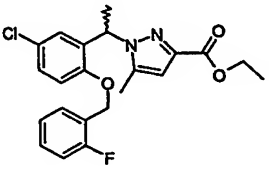
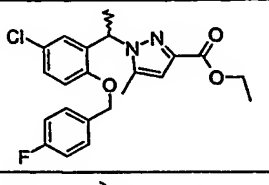
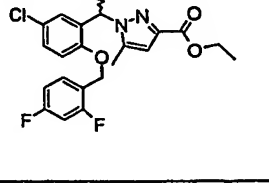
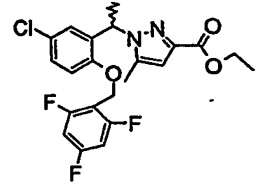
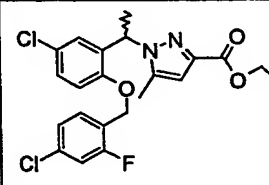
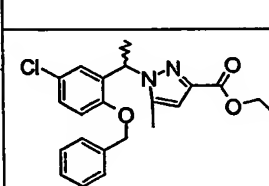
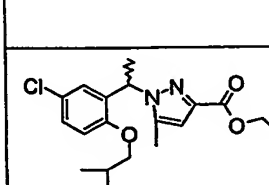
A mixture of 1-[1-(5-chloro-2-hydroxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (100mg, 0.32mmol), K_2CO_3 (112mg, 0.81mmol) and 2-chloro-4-fluorobenzyl bromide (79mg, 0.36mmol) in acetone (3ml) was refluxed overnight under nitrogen. After cooling the solid was filtered off and the solvent removed in vacuo.

Purification was carried out on a SPE using iso-hexane containing a gradient of ethyl acetate (5-10%) to yield the title compound (120mg, 74%).

30

$t = 3.95$, $[\text{MH}^+]$ 451,454.

The following 1H-pyrazole-3-carboxylic acid esters were prepared from G according to Method 5

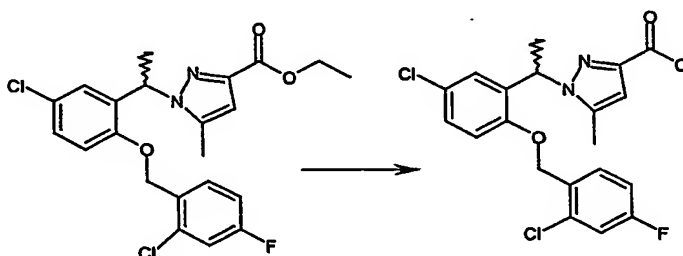
	Name	1-{5-chloro-2-[(2-fluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.78, [MH ⁺] 417,419
	Method	G and Method 5
	Name	1-{5-chloro-2-[(4-fluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.77, [MH ⁺] 417,419
	Method	G and Method 5
	Name	1-{5-chloro-2-[(2,4-difluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.80, [MH ⁺] 435,437 [MH ⁻] 433
	Method	G and Method 5
	Name	1-{5-chloro-2-[(2,4,6-trifluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.58, [MH ⁺] 453,455
	Method	G and Method 5
	Name	1-{5-chloro-2-[(4-chloro-2-fluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.96, [MH ⁺] 451,454
	Method	G and Method 5
	Name	1-{5-chloro-2-[(benzyloxy)-phenyl]-ethyl}-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.77, [MH ⁺] 399,401
	Method	G and Method 5
	Name	1-[1-(5-chloro-2-isobutoxy-phenyl)-ethyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid ethyl ester
	LCMS	<i>t</i> = 3.88, [MH ⁺] 365,367
	Method	see below

5 Preparation of 1-[1-(5-chloro-2-isobutoxy-phenyl)-ethyl]-5-methyl-1*H*-pyrazole-3-carboxylic acid ethyl ester

A mixture of 1-[1-(5-chloro-2-hydroxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (100mg, 0.32mmol), K₂CO₃ (112mg, 0.81mmol) and 1-bromo-2-methylpropane (0.038ml, 0.36mmol) in DMF (3ml) was heated at 80°C under nitrogen for 2 hours. After cooling the solution was diluted with water and extracted with ethyl acetate (3 x 10ml). The combined extracts were dried (MgSO₄) and evaporated. Purification was carried out on a SPE (20% ethyl acetate :iso-hexane) to yield the title compound.
 t = 3.88, [MH⁺] 365, 367

General Method 6

Example 50: 1-{1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid



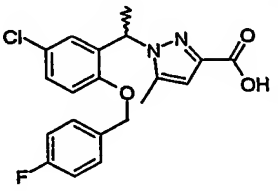
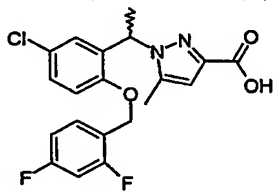
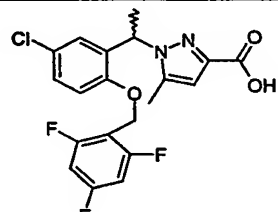
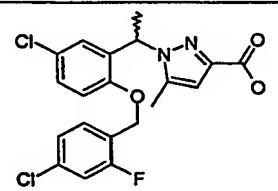
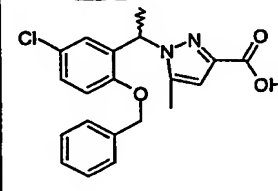
To a solution of 1-{1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid ethyl ester (120mg, 0.26mmol) in 3 ml of ethanol and 1ml of water, NaOH (42mg, 1.06mmol) was added. The mixture was stirred at 60°C for 2 hours. the solution was diluted with water, acidified with acetic acid and extracted with ethyl acetate. The organic solution was dried over MgSO₄ and evaporated to give the title compound (112mg, 99%).

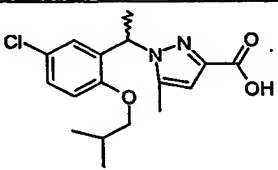
¹H NMR (DMSO) δ: 1.67 (3H, bs), 1.94 (3H, s), 5.21 (2H, s), 5.66 (1H, q, J=6.8 Hz), 6.12 (1H, s), 6.82 (1H, d, J=2.6 Hz), 7.18 (1H, d, J=8.8 Hz), 7.19-7.31 (2H, m), 7.56 (1H, dd, J=2.6 J=8.8 Hz), 7.64 (1H, m).

t = 3.76, [MH⁻] 421, 424.

The following Examples were prepared from the appropriate ester intermediate according to Method 6

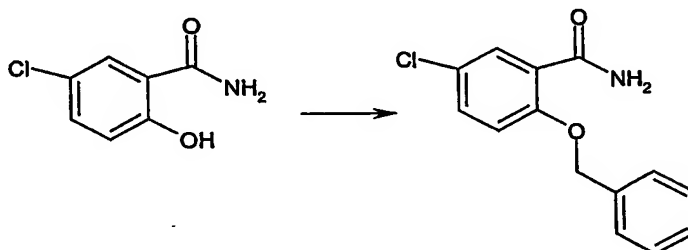
51		Name	1-{5-chloro-2-[(2-fluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: (DMSO) 1.68 (3H, d, J=6.8 Hz), 2.01 (3H, s), 5.17-5.24 (2H, m), 5.77 (1H, q, J=6.8 Hz), 6.43 (1H, s), 6.93 (1H, d, J=2.6 Hz), 7.2-7.5 (6H, m), 12.6 (1H,bs).
		LCMS	t = 3.59, [MH ⁺] 389 [MH ⁻] 387, 389
		Method	Method 6

52		Name	1-{5-chloro-2-[(4-fluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: (DMSO) 1.68 (3H, d, J=6.8 Hz), 2.0 (3H, s), 5.17 (2H, s), 5.73 (1H, q, J=6.8 Hz), 6.26 (1H, s), 6.88 (1H, d, J=2.6 Hz), 7.13 (1H, d, J= 8.8 Hz), 7.12-7.32 (3H, m), 7.46-7.5 (2H, m).
		LCMS	t = 3.56, [MH ⁺] 389 [MH ⁻] 387, 389
		Method	Method 6
53		Name	1-{5-chloro-2-[(2,4-difluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: (DMSO) 1.66 (3H, d, J=6.8 Hz), 2.0 (3H, s), 5.2 (2H, s), 5.63 (1H, q, J=6.8 Hz), 6.14 (1H, s), 6.82 (1H, d, J=2.6 Hz), 7.12-7.21 (2H, m), 7.28-7.37 (2H,m), 7.60 (1H, q, J=6.8 Hz).
		LCMS	t = 3.61, [MH ⁺] 407, 409 [MH ⁻] 405, 407
		Method	Method 6
54		Name	1-{5-chloro-2-[(2,4,6-trifluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: (DMSO) 1.63 (3H, d, J=6.8 Hz), 1.96 (3H, s), 5.14 (2H, q, J=11 Hz), 5.65 (1H, q, J=6.8 Hz), 6.37 (1H, s), 6.96 (1H, s), 7.25-7.39 (4H, m).
		LCMS	t = 3.58, [MH ⁺] 425,427 [MH ⁻] 423,425
		Method	Method 6
55		Name	1-{5-chloro-2-[(4-chloro-2-fluorobenzoyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: (DMSO) 1.68 (3H, d, J=6.8 Hz), 1.97 (3H, s), 5.21 (2H, s), 5.67 (1H, q, J=6.8 Hz), 6.18 (1H, s), 6.82 (1H, d, J=2.6 Hz), 7.17 (1H, d, J=8.8 Hz), 7.24-7.38 (2H, m), 7.50-7.62 (2H, m).
		LCMS	t = 3.83, [MH ⁻] 421
		Method	Method 6
56		Name	1-{5-chloro-2-[(benzyloxy)-phenyl]-ethyl}-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	¹ H NMR δ: (DMSO) 1.68 (3H, bs), 2.1 (3H, s), 5.21 (2H, s), 5.75 (1H, q, J=6.8 Hz), 6.2 (1H, s), 6.82 (1H, d, J=2.6 Hz), 7.15 (1H, d, J=8.8 Hz), 7.21-7.5 (6H, m).
		LCMS	t = 3.58, [MH ⁺] 371
		Method	Method 6

57		Name	1-[1-(5-chloro-2-isobutoxy-phenyl)-ethyl]-5-methyl-1H-pyrazole-3-carboxylic acid
		NMR	^1H NMR δ : (DMSO) 0.98 (6H, t, $J=7.08$ Hz), 1.71 (3H, d, $J=6.88$ Hz), 2.02-2.06 (1H, m), 2.18 (3H, s), 3.80 (2H, d, $J=6.36$ Hz), 5.83-5.87 (1H, m), 6.52 (1H, s), 6.85 (1H, d, $J=2.6$ Hz), 7.04 (1H, d, $J=8.8$ Hz), 7.3 (1H, dd, $J=8.7$, $J=2.6$ Hz), 12.6 (1H, bs).
		LCMS	$t = 3.65$, $[\text{MH}^+]$ 337
		Method	Method 6

Preparation of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (H)

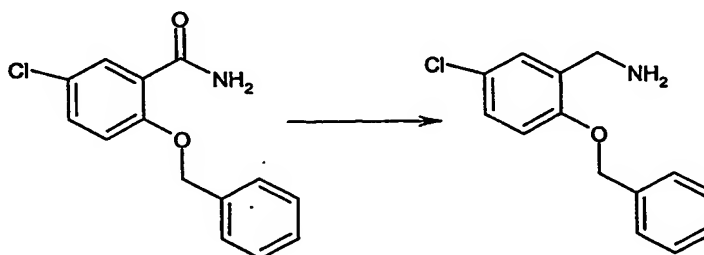
Preparation of 2-benzyloxy-5-chloro-benzamide



- 10 A mixture of 5-chloro-2-hydroxy-benzamide (8g, 0.046mol), K_2CO_3 (7.72g, 0.056mol) and benzyl bromide (6.1ml, 0.051mol) in acetone (50ml) was refluxed overnight, under nitrogen. After cooling, the solid was filtered off and the filtrate was cooled (in a fridge) to effect crystallisation. The resultant solid was collected to give 9.9g (81%) of a colourless solid.

15 $t = 2.90$, $[\text{MH}^+]$ 262, 264

Preparation of 2-benzyloxy-5-chloro-benzylamine

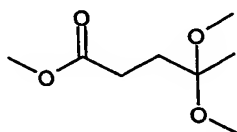


- 20 2-benzyloxy-5-chloro-benzamide (7.9g, 0.030mol) in 20ml of tetrahydrofuran was slowly added, under nitrogen, to a 1M solution of LiAlH_4 (45ml) in tetrahydrofuran at 0°C . The reaction mixture was then heated at 70°C for 1hour. After cooling the reaction mixture was

poured onto water and extracted with ethyl acetate (3 x 40ml). The combined extracts were dried (MgSO_4) and evaporated to give the title compound as a yellow oil (7g, 94%).
 ^1H NMR δ : 1.66 (2H, bs), 3.84 (2H, s), 5.07 (2H, s), 6.83 (1H, d, $J=8.6\text{Hz}$), 7.15 (1H, dd, $J=8.6$ and 2.6Hz), 7.24-7.42 (6H, m).

5

Preparation of 4,4-dimethoxy-pentanoic acid methyl ester



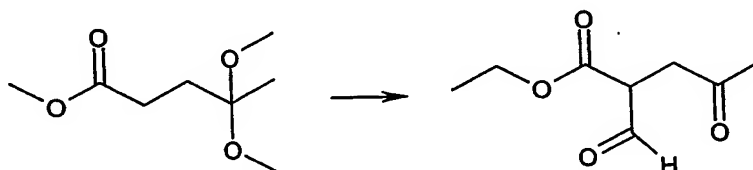
10

Ethyl levulinate (20g, 0.138mol), trimethyl orthoformate (15.3g, 0.144mol) and a catalytic amount of *p*-toluene sulfonic acid monohydrate in 6 ml of methanol were refluxed over the weekend. After cooling the mixture was vacuum down and the residue used with no further purifications.

^1H NMR δ : 1.25 (3H, bs), 1.94-1.98 (2H, m), 2.32-2.37 (2H, m), 3.17 (6H, s), 3.68 (3H, s).

15

Preparation of 2-formyl-4-oxo-pentanoic acid ethyl ester



20

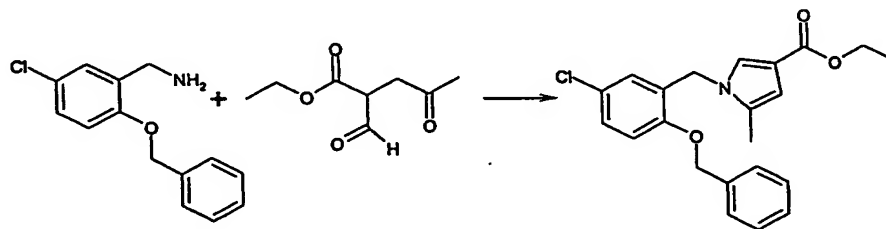
A mixture of 4,4-dimethoxy-pentanoic acid methyl ester (25g, 0.13mol) and ethyl formate (21ml, 0.26mol), was added to a solution of NaH (5.78g, 0.144mol) in THF (50ml) at $\sim 10^\circ\text{C}$. The reaction mixture was stirred for 3h, then let stand overnight. Water (100ml) and ether (60ml) were added and the mixture stirred for 5 minutes. The organic phase was then separated and washed with water. The combined water layers were acidified to pH 2 and extracted with ethyl acetate (3x50ml). The combined extracts were dried (MgSO_4) and evaporated. The residue was then distilled, the fraction with b.p. $110-120^\circ\text{C}$ was the desired compound.

25

^1H NMR δ : 1.27-1.32 (3H, m), 2.23 (3H, s), 2.63 (1H, t, $J=6.7\text{Hz}$), 2.76 (1H, t, $J=6.7\text{Hz}$), 3.78-3.81 (1H, m), 4.19-4.28 (2H, m), 9.93 (1H, s).

30

Preparation of 1-(2-benzyloxy-5-chloro-benzyl)-5-methyl-1H-pyrrole-3 carboxylic acid ethyl ester

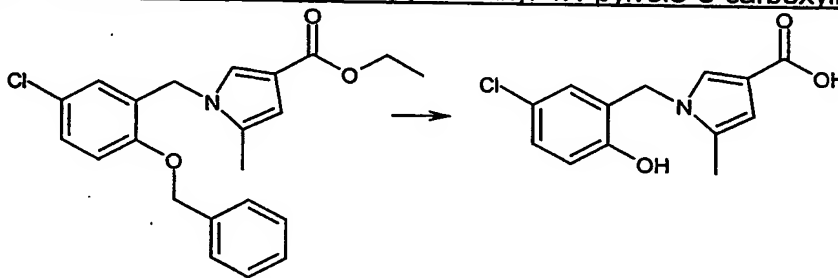


To a mixture of 2-formyl-4-oxo-pentanoic acid ethyl ester (2.5g, 0.016mol) and

2-benzyloxy-5-chloro-benzylamine (4.7g, 0.019mol), CH₃COOH (~3ml) was added. The reaction mixture was stirred for 2 hours then was poured onto water and extracted with ethyl acetate (3 x 40ml). The combined extracts were dried (MgSO₄) and evaporated. The residue was purified on a Biotage (15% ethyl acetate:iso-hexane) to give the title compound as a yellow solid (2.8g, 45%).

¹H NMR δ: 1.32 (3H, t, J=7.1Hz), 2.08 (3H, s), 4.25 (2H, q, J=7.1Hz), 4.98 (2H, s), 5.07 (2H, s), 6.35 (1H, s), 6.61 (1H, s), 6.87 (1H, d, J=8.7Hz), 7.18-7.21 (2H, m), 7.33-7.41 (5H, m).

10 Preparation of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1H-pyrrole-3-carboxylic acid

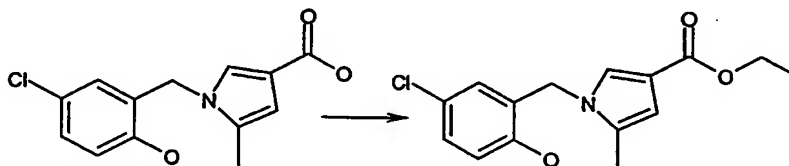


A mixture of sodium methanethiolate (1.16g, 16.5mmol) and 1-(2-benzyloxy-5-chloro-benzyl)-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester

(1.27g, 3.3mmol) in DMF (14ml) was stirred at 100°C for 3 hours. After cooling the mixture was diluted with water and acidified with 1M HCl and then extracted with ethyl acetate. The organic phase was dried (MgSO₄), evaporated to dryness to give the title compound as a yellow oil.

t = 2.76, [MH⁺] 266 [MH⁻] 264.

20 Preparation of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester



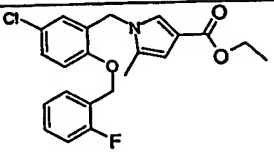
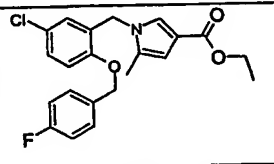
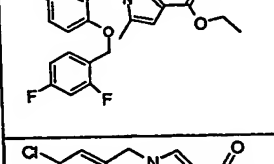
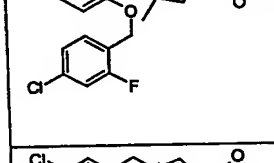
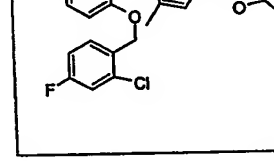
A mixture of 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1H-pyrrole-3-carboxylic acid (3.3mmol) and H₂SO₄ (1.5ml) in ethanol (15ml) was refluxed overnight.

25 After cooling the mixture was diluted with water basified with NH₃ and then extracted with ethyl acetate (3x20ml). The combined organic layers were dried (MgSO₄), and the solvent removed *in vacuo*. Purification was carried out on a SPE using 30% ethyl acetate in iso-hexane to yield the title compound as a yellow solid (0.73g, 75%).

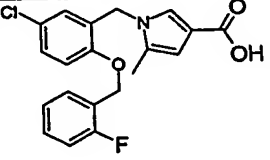
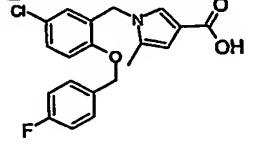
t = 3.28, [MH⁺] 294, 296 [MH⁻] 292.

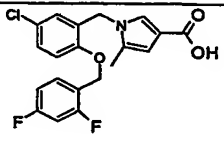
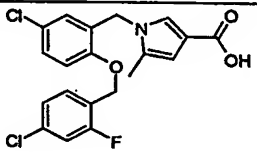
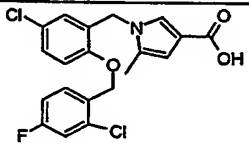
30

The following intermediates were prepared from 1-(5-chloro-2-hydroxy-benzyl)-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (intermediate H) according to Method 5.

	Name	1-[5-chloro-2-(2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 3.92, [MH ⁺] 402,404
	Method	H and Method 5
	Name	1-[5-chloro-2-(4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 3.91, [MH ⁺] 402,404
	Method	H and Method 5
	Name	1-[5-chloro-2-(2,4-difluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 3.93, [MH ⁺] 420,422
	Method	H and Method 5
	Name	1-[5-chloro-2-(4-chloro-2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 4.09, [MH ⁺] 436,439
	Method	H and Method 5
	Name	1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid ethyl ester
	LCMS	t = 4.08, [MH ⁺] 436,439
	Method	H and Method 5

The following Examples were prepared from the appropriate ester intermediate according to Method 6.

58		Name	1-[5-chloro-2-(2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	¹ H NMR (DMSO)δ: 1.99 (3H, s), 5.03 (2H, s), 5.23 (2H, s), 6.15 (1H, s), 6.62 (1H, s), 7.21-7.29 (5H, m), 7.36 (1H, d, J=8 Hz), 7.41-7.45 (1H, m), 7.53 (1H, t, J=7.4 Hz), 11.6 (1H, s).
		LCMS	t = 3.50, [MH ⁺] 374,376 [MH ⁻] 372,374
		Method	Method 6
59		Name	1-[5-chloro-2-(4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	¹ H NMR (DMSO)δ: 2.03 (3H, s), 5.07 (2H, s), 5.17 (2H, s), 6.17 (1H, s), 6.64 (1H, s), 7.14-7.23 (3H, m), 7.29 (1H, s), 7.33 (1H, bd), 7.47-7.5 (2H, m), 11.59 (1H, s).
		LCMS	t = 3.48, [MH ⁺] 374,376 [MH ⁻] 372,374
		Method	Method 6

60		Name	1-[5-chloro-2-(2,4-difluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	¹ H NMR (DMSO)δ: 1.99 (3H, s), 5.02 (2H, s), 5.19 (2H, s), 6.15 (1H, s), 6.64 (1H, s), 7.08-7.14 (1H, m), 7.21-7.38 (4H, m), 7.58-7.65 (1H, m), 11.6 (1H, s).
		LCMS	t = 3.48, [MH ⁺] 392,394 [MH ⁻] 390,392
		Method	Method 6
61		Name	1-[5-chloro-2-(4-chloro-2-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	¹ H NMR (DMSO)δ: 2.0 (3H, s), 5.03 (2H, s), 5.21 (2H, s), 6.16 (1H, s), 6.63 (1H, s), 7.21 (1H, d, J=8.8 Hz), 7.28 (1H, s), 7.31-7.37 (2H, m), 7.5-7.58 (2H, m), 11.6 (1H, s).
		LCMS	t = 3.70, [MH ⁺] 408,411 [MH ⁻] 406,410
		Method	Method 6
62		Name	1-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-benzyl]-5-methyl-1H-pyrrole-3-carboxylic acid
		NMR	¹ H NMR (DMSO)δ: 1.99 (3H, s), 5.06 (2H, s), 5.21 (2H, s), 6.16 (1H, s), 6.63 (1H, s), 7.19-7.28 (3H, m), 7.37 (1H, bd), 7.55 (1H, bd), 7.6-7.68 (1H, m), 11.6 (1H, s).
		LCMS	t = 3.70, [MH ⁺] 408,411 [MH ⁻] 406,409
		Method	Method 6

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

5

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP₁, EP₂, EP₃, EP₄, FP, IP and TP.

10

Biological Activity at EP₁ and EP₃ Receptors

The ability of compounds to antagonise EP₁ & EP₃ receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ([Ca²⁺]_i) in response to activation of EP₁ or EP₃ receptors by the natural agonist hormone prostaglandin E₂ (PGE₂). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE₂ can mobilise. The net effect is to displace the

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PGE₂ concentration-effect curve to higher concentrations of PGE₂. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of [Ca²⁺]_i produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP₁ or EP₃ calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP₁ or EP₃ cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10µg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE₂ are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE₂ (pIC₅₀) may then be estimated.

Binding Assay for the Human Prostanoid EP₁ Receptor

Competition assay using [³H]-PGE₂.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E₂ ([³H]-PGE₂) for binding to the human EP₁ receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP₁ cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10µg/ml puromycin and 10µM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid

(Na₂EDTA) and 10µM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na₂EDTA, 140mM NaCl, 10µM indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed three times by suspension and centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na₂EDTA, 10mM MgCl₂ (pH 6). Aliquots are frozen at -80°C until required.

- 10 For the binding assay the cell membranes, competing compounds and [³H]-PGE₂ (3nM final assay concentration) are incubated in a final volume of 100µl for 30 min at 30°C. All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding (IC₅₀).

Biological Activity at TP Receptor

- To determine if a compound has agonist or antagonist activity at the TP receptor a functional calcium mobilisation assay may be performed. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ([Ca²⁺]_i) in response to activation of TP receptors by the stable TXA₂ mimetic U46619. Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of U46619 can mobilise. The net effect is to displace the U46619 concentration-effect curve. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of [Ca²⁺]_i produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software. The agonist activity of the compounds are determined by their ability to cause an increase in intracellular mobilisation in the absence of U46619.

- The human TP calcium mobilisation assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing TP cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10µg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 96-well plate. Following incubation for 24 hours at 37°C the culture media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of U46619 are then added to the plate in order to assess the antagonist properties of the compounds.

10 The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by U46619 (IC_{50}) may then be estimated, and the percentage activation caused by the compounds directly can be used to determine if there is any agonism present.

15 By application of these techniques, compounds of the Examples had an antagonist IC_{50} value of between 7.0 and 10.0 at EP_1 receptors and IC_{50} value of < 5.7 at EP_3 receptors.

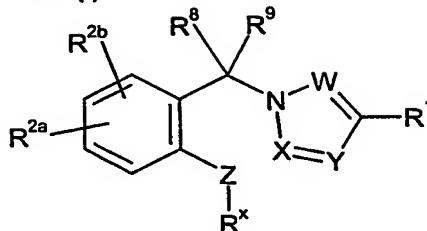
The Examples had antagonist IC_{50} value of between 5.0 and 10.0 at TP receptors.

20 No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

25 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

- 5 wherein:

W represents N or CR¹⁰ wherein R¹⁰ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;

X represents N or CR¹¹ wherein R¹¹ represents hydrogen, halogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heterocyclyl;

- 10 Y represents N or CR¹² wherein R¹² represents hydrogen, halogen, CH₃ or CF₃;

Z represents O, S, SO or SO₂;

R¹ represents CO₂R⁴, CONR⁵R⁶, CH₂CO₂H, optionally substituted SO₂alkyl, SO₂NR⁵R⁶, NR⁵CONR⁵R⁶, 2H-tetrazol-5-yl-methyl or optionally substituted heterocyclyl;

- 15 R^{2a} and R^{2b} independently represents hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, CN, SO₂alkyl, SR⁵, NO₂, optionally substituted aryl, CONR⁵R⁶ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR⁴, O and SO_n, wherein n is 0, 1 or 2; or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally

- 20 substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

R⁴ represents hydrogen or an optionally substituted alkyl;

R⁵ represents hydrogen or an optionally substituted alkyl;

R⁶ represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO₂aryl, optionally substituted SO₂alkyl, optionally substituted

- 25 SO₂heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR⁷;

R⁷ represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;

R⁸ and R⁹ are independently selected from hydrogen, fluorine or alkyl, or R⁸ and R⁹

- 30 together with the carbon to which they are attached form a cycloalkyl ring, optionally containing up to one heteroatom selected from O, S, NH or N-alkyl;

wherein Q^a and Q^b are each independently selected from hydrogen, CH₃ and fluorine; or a derivative thereof.